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The American Journal of Medicine

Vol. XVII SEPTEMBER, 1954 No. 3

Editorial

Ballistocardiography . . . . . A. McGehee Harvey 295

Clinical Studies

Syndrome of Patent Ductus Arteriosus with Reversal of Flow
Daniel S. Lukas, Jorge Araujo and Israel Steinberg 298

In a paper of unusual interest, the authors describe the clinical and hemodynamic characteristics of patent ductus arteriosus with reversal of flow and sufficient shunting of blood from pulmonary artery to aorta, at least upon exercise, to cause perceptible cyanosis. This may occur without congestive failure; when it does the continuous murmur of patent ductus is obliterated, and a variety of extraordinary symptoms and signs appear which would otherwise be most difficult to understand. The site of the shunt favors distribution of the venous admixture, except for retrograde flow, to the legs and left arm, causing more pronounced cyanosis and clubbing of the toes than the fingers, and sometimes unequal distribution in the two hands. Angiocardiographic and catheterization data are decisive in diagnosis. Surgical correction is extremely hazardous.

Pulmonary Stenosis with Left to Right Shunt
Oscar Magidson, Richard S. Cosby, Sim P. Dimitroff, David C. Levinson and George C. Griffith 311

This study deals with a group of cases presenting pulmonary stenosis of mild or moderate degree, with little or no increase in right atrial and right ventricular diastolic pressure, associated with atrial septal defect, ventricular septal defect or transposed pulmonary veins permitting a left to right shunt. The clinical and hemodynamic characteristics of this group are described and contrasted with the findings in more severe degrees of pulmonary stenosis with reversed interatrial shunt. The question of the inadvisability of pulmonary valvulotomy in these cases is discussed.

Some Variations in the Clinical Picture of Congenital Defect of the Interventricular Septum . . . . . Noble O. Fowler 322

A concise report of seven cases in which, despite considerable variation in manifestations, a diagnosis of interventricular septal defect was made largely on the basis of cardiac catheterization data. An eighth patient suggested interventricular septal defect clinically but the catheterization data indicated tetralogy of Fallot.

Myocardial Ischemia during Mitral Commissurotomy
J. Gerard Mudd, John J. Inkley and C. Rollins Hanlon 330

This study offers additional evidence for the importance of constant electrocardiographic monitoring during cardiac surgery, particularly during application of auricular clamps in the course of

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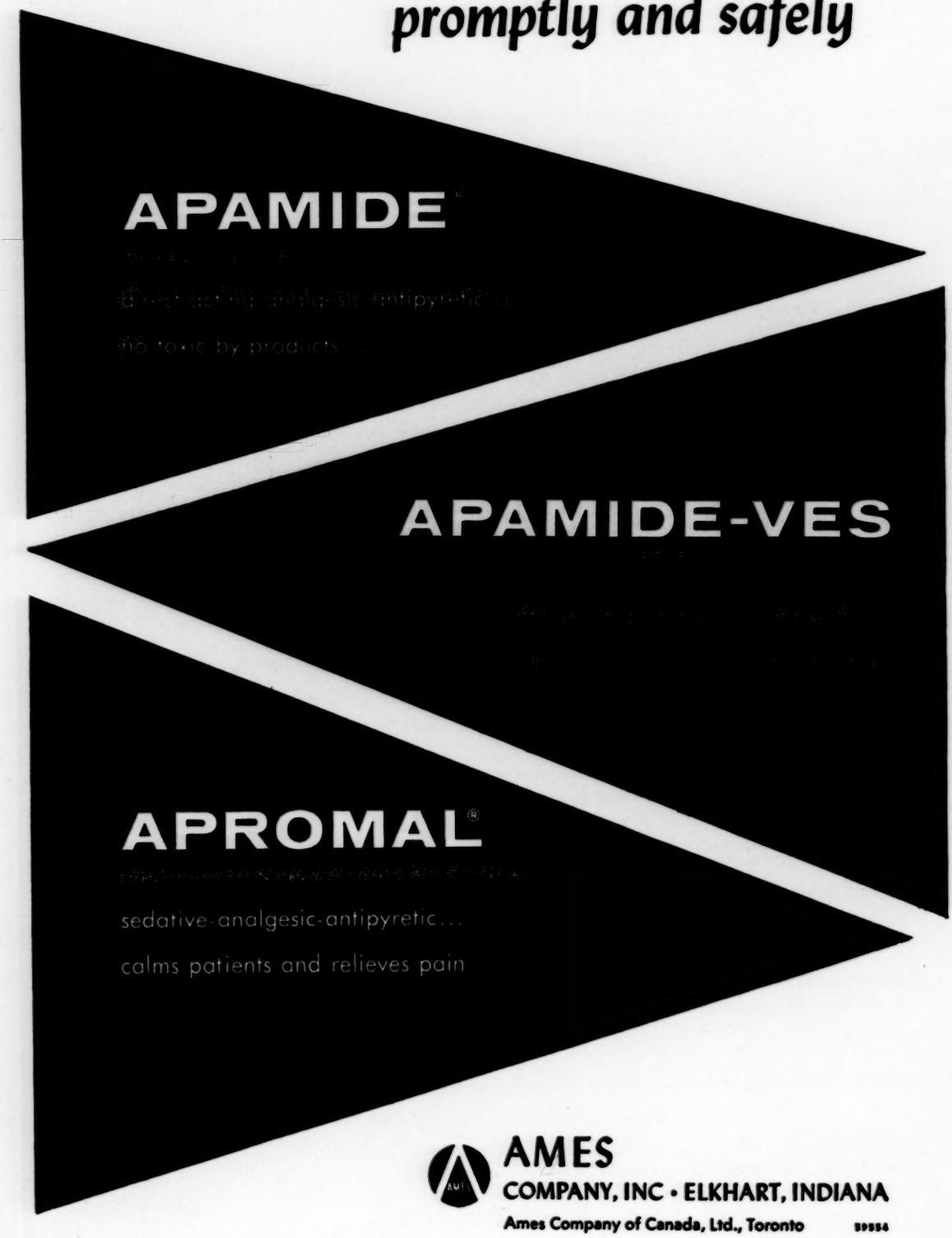
relieve pain, headache, fever promptly and safely



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mitral commissurotomy. Among the interesting electrocardiographic changes recorded was the appearance of Q waves in conventional leads, simulating myocardial infarction but of transitory nature. This observation again raises questions concerning the significance of the Q wave and points up the value of such records, made during direct manipulation of the human heart, for interpretation of electrocardiograms.

Histogenesis of Arteriosclerosis of the Larger Cerebral Arteries, with an Analysis of the Importance of Mechanical Factors

HERMAN T. BLUMENTHAL, FRED P. HANDLER AND J. OWEN BLACHE 337

The particular liability of the larger cerebral arteries to arteriosclerosis, and the importance of the clinical consequences of such involvement, lend special interest to this unusually detailed morphologic study of these arteries. It is made clear that the vessels composing the circle of Willis have intrinsic peculiarities in structure and development which make them especially vulnerable to aneurysmal dilatation and rupture. It is inferred by the authors that the development of arteriosclerosis may therefore, in this area at least, represent an adaptive response to hydrostatic pressure. Whether such an arteriosclerotic response is purposeful or disadvantageous is open to question.

Blood Lipid Levels As Influenced by Weight Reduction in Women

NORMAN S. MOORE, CHARLOTTE M. YOUNG AND LEONARD A. MAYNARD 348

In this study of the effect in normal women of weight reduction induced by caloric restriction without extreme reduction in fat intake, there was, if anything, a slight mean increase in serum cholesterol and phospholipid. The most significant observation, however, was confirmation of the known regular cyclic variations in blood lipids in normal human subjects. In women these appear to be particularly marked and may be related in some way to the menstrual cycle. It follows that assessment of the effects of drugs or diets upon the blood lipids should be based upon observations of sufficient duration, with an adequate baseline of measurements during the control period.

Studies on the Adrenal Zona Glomerulosa of Hypertensive Patients and Rats. With Special Reference to the Effect of Dietary Salt Restriction

ERNST PESCHEL AND GEORGE J. RACE 355

An interesting study indicating that in man, as in the rat, marked restriction of sodium intake results in a widening of the zona glomerulosa of the adrenals, the area generally held to elaborate the corticoids chiefly responsible for regulation of the metabolism of sodium and other electrolytes. This implies increased production of such hormones under these circumstances.

Variability of the Rate of Coagulation of Whole Blood

JEROME M. WALDRON AND GARFIELD G. DUNCAN 365

Measurement of the clotting time of whole blood, performed quite casually in most laboratories, is

Contents continued on page 7

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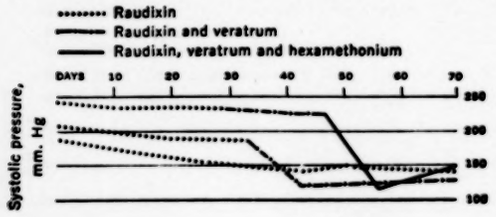

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SQUIBB

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2. FREIS, E. D.: M. CLIN. NORTH AMERICA 38:363, 1954.

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subject to large variation due to innumerable factors, as this study makes clear. The article also provides the authors with opportunity to reply to recent criticisms of their claims in respect to the effects of fat ingestion on clotting.

Review

Primary Thrombosis of the Internal Carotid Artery. Report of Seven Cases with Cerebral Circulatory and Metabolic Studies

LAMAR OCHS, WILLIS SENSENBACH AND LEONARD MADISON 374

The authors review the current status of "primary" thrombosis of the internal carotid artery, an entity much neglected by pathologist as well as clinician, and add seven new cases. This disorder may be responsible for bizarre and puzzling disturbances in vision, together with neurologic symptoms and signs simulating brain tumor, hence deserves more attention. The authors studied the cerebral hemodynamics in their cases but found such deviations as could be detected to be within the normal variation of the age periods studied; however, if carotid ligation is contemplated, these measurements help to assess the risk. The futility of establishment of a cervical arteriovenous fistula was reaffirmed.

Seminars on Antihypertensive Drugs

Management of Hypertensive Disease

A. C. CORCORAN, H. P. DUSTAN, R. D. TAYLOR AND IRVINE H. PAGE 383

The authors, in this contribution, give a sober estimate of their experience with the several available modes of management of hypertensive disease, referring in particular to the use of antipressor drugs given separately and in combination. Their enthusiasm is distinctly restrained in view of the limitations of therapy and the frequency of side reactions with the more potent agents such as the veratrum alkaloids, hydralazine and the ganglion blockers. Nevertheless, the net advance is conceded to be encouraging, particularly in respect to the use of Rauwolfia preparations and the judicious use of certain combinations. Because of its broad scope and constant awareness of basic therapeutic principles, this article will be found to be of special interest.

Conference on Therapy

A Re-evaluation of Quinidine Therapy 395

Conference on Therapy (Cornell University Medical College)—Debate concerning the use and usefulness of quinidine in the control of cardiac arrhythmias continues, with almost as many shades of opinion as there are prescribers. In this conference, Dr. Gold, an enthusiastic proponent of the drug, expresses his views regarding indications for administration of quinidine, the optimum

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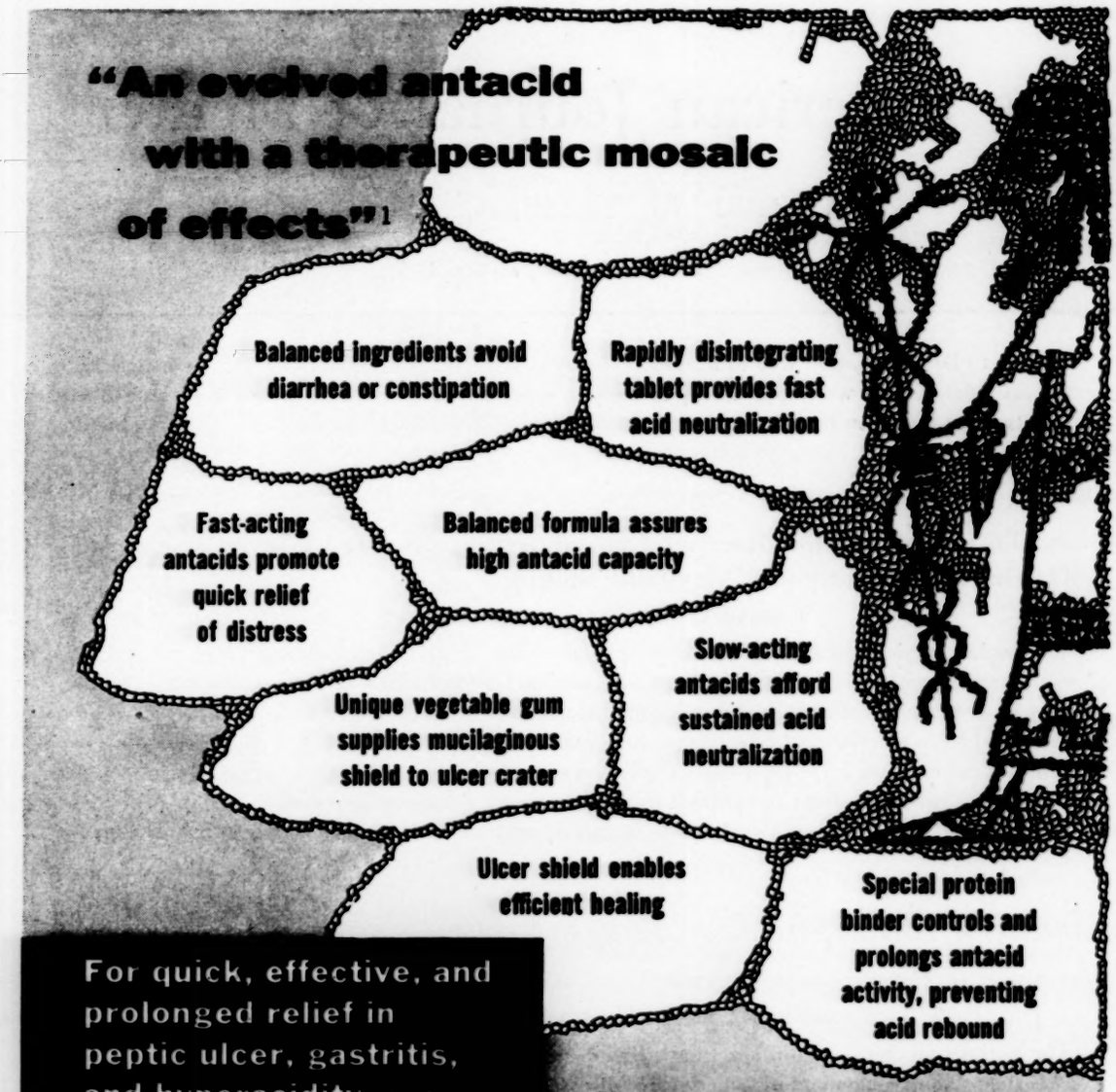
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[1]C. S. DeCourcy, and C. Rosenberg, Staff, Dept. DeCourcy Clinic, 28, June 15, 1954

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dosage schedule for treatment of paroxysmal arrhythmias and for prevention of recurrences, the dangers in establishment of a normal rhythm by quinidine particularly in the presence of heart block, the problem of concurrent use of digitalis and quinidine, etc. A lively and informative discussion ensues, with Dr. Gold seemingly largely on the defensive.

Clinico-pathologic Conference

Hyperthyroidism, Possible Malignancy, Liver Disease and Therapeutic Myxedema . 403

Clinico-pathologic Conference (Washington University School of Medicine)—In this case, what began as a quite typical instance of hyperthyroidism developed features that proved difficult of analysis even with modern methods of laboratory diagnosis. The discussion and findings illuminate many aspects of diagnosis and management of diseases of the thyroid gland.

Case Reports

Quinidine-induced Thrombocytopenic Purpura. Report of a Fourteenth Case and Review of Clinical and Experimental Studies

LOUIS WEISFUSE, PAUL W. SPEAR AND MARTIN SASS 414

An informative and well studied case of quinidine-induced thrombocytopenic purpura, applying modern *in vitro* technic to demonstrate platelet agglutinins. The procedure should be extended to more cases of secondary thrombocytopenic purpura.

Erythrophagocytosis and Thrombocytopathy Occurring during the Course of a Henoch-Schönlein Syndrome Due to Quinine

CAPTAIN WILLIAM P. CREGER AND CAPTAIN JOHN H. HOUSEWORTH 423

An interesting and well studied case of quinine hypersensitivity exhibiting the Henoch-Schönlein syndrome accompanied by immunohematologic phenomena indicating specific antibody activity, including erythrophagocytosis.

Primary Carcinoma of the Liver with Early Metastasis to the Spine and Initial Symptoms of Paraplegia . . . . . R. D. TREVATHAN 432

An unusual case.

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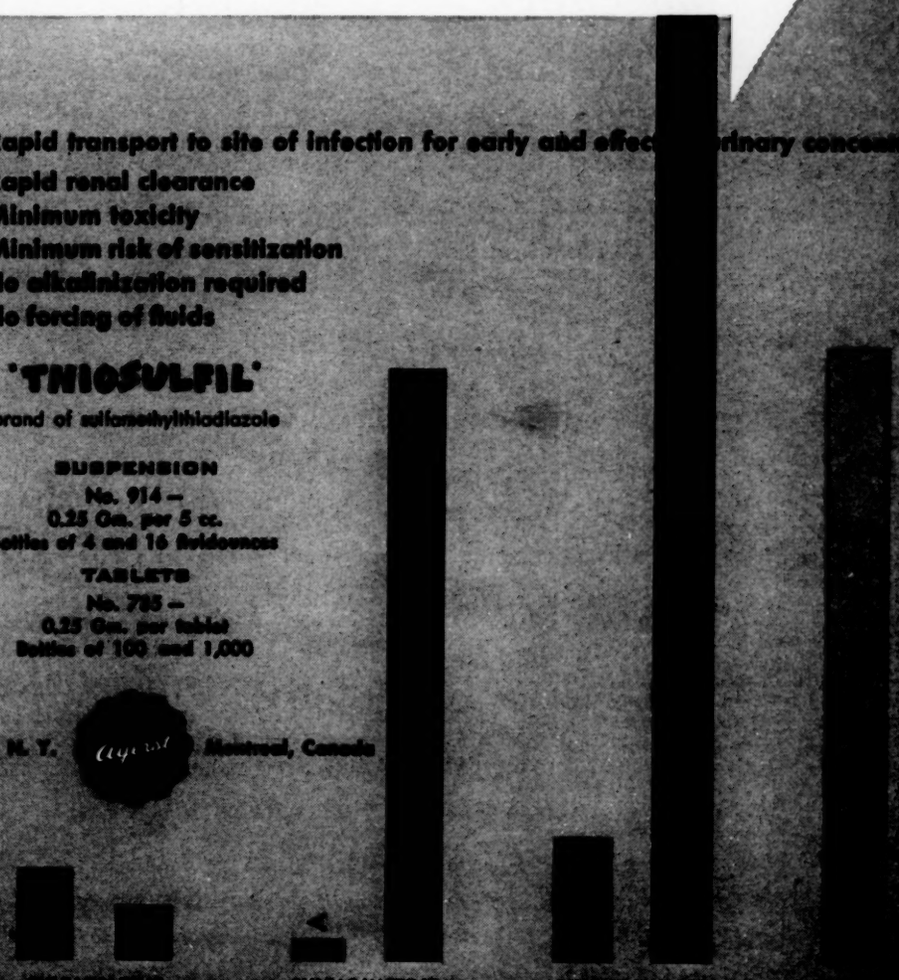

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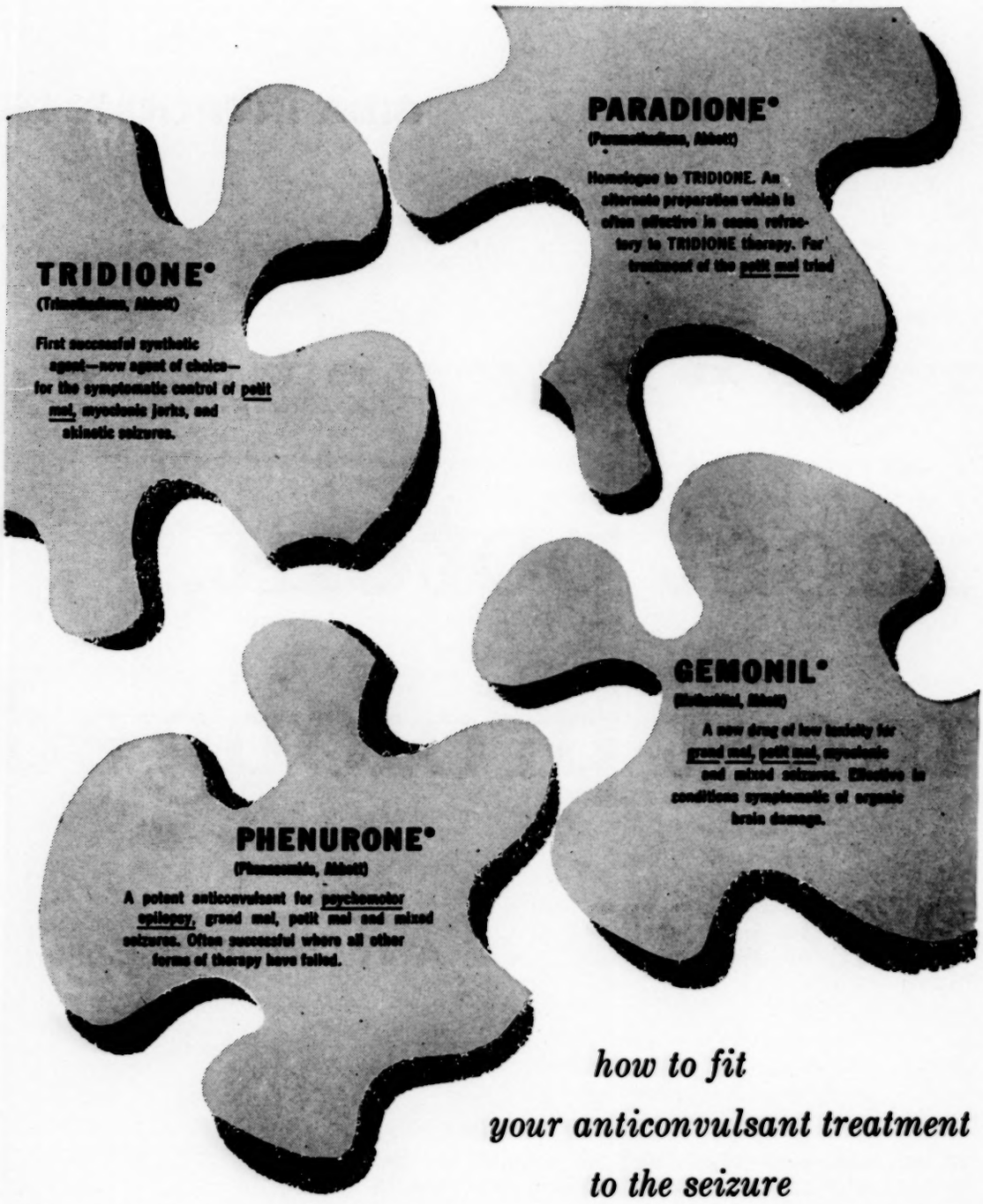
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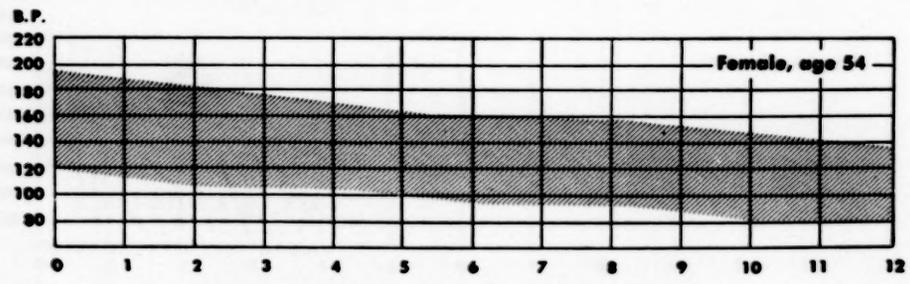

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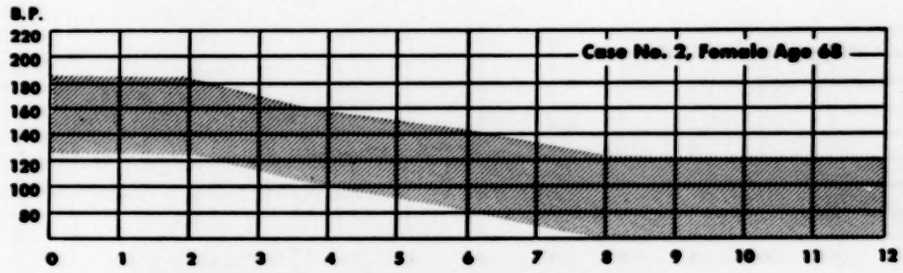

Weeks of therapy. Rauvera, 4 tablets daily. Note blood pressure response.

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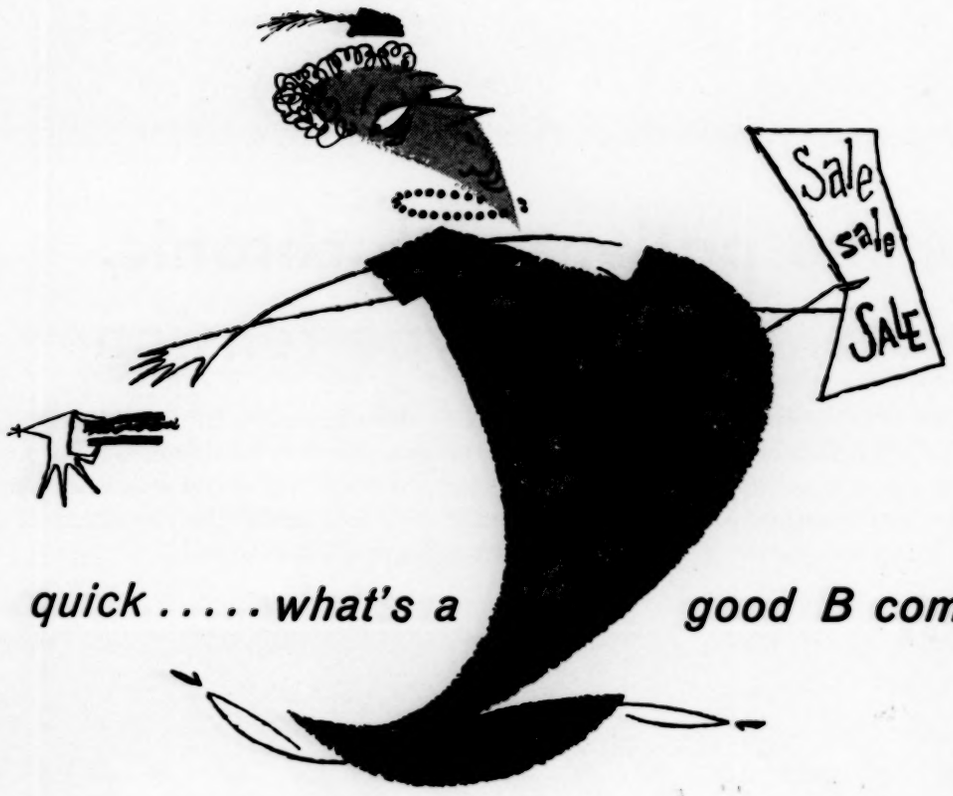

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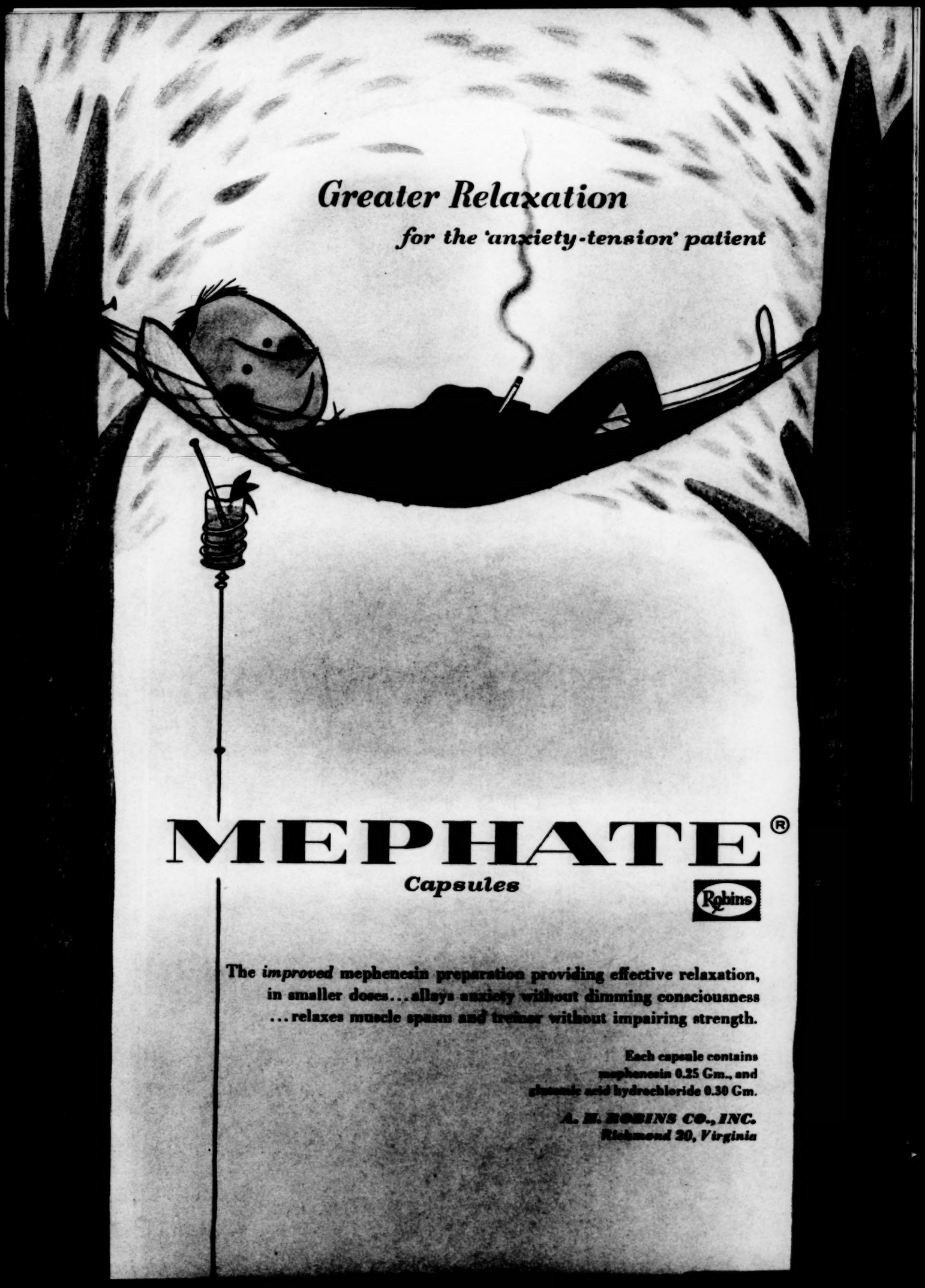
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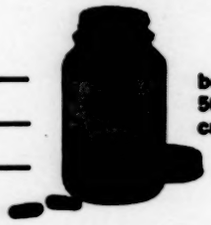

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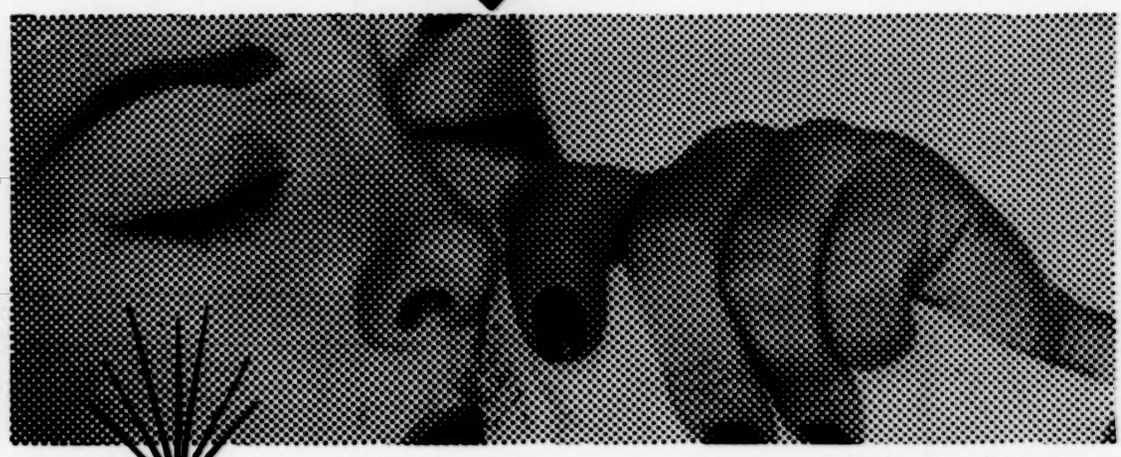

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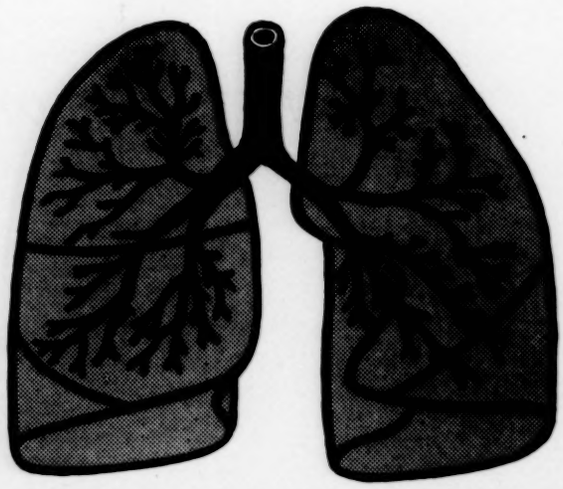

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Editorial

Ballistocardiography*

BALLISTOCARDIOGRAPHY is a medical technic of disputed value. The literature pertaining to this field is rapidly expanding and many of the opinions expressed contradict one another. The technic appeals to the average physician because of its simplicity and because it provides a kind of information about the circulation not supplied by other methods. The widespread use of the ballistocardiograph both in the care of patients and in clinical investigation suggests that a fresh assessment of its value and limitations may be timely. It seems likely that ballistocardiography will have an important future, provided its progress is not retarded by distrust resulting from claims that have not been substantiated by scientific testing.

The technic of ballistocardiography aims at measuring the strength or force of cardiac ejection by recording the body motions produced by this event. Progress in this methodology has been slow because of three barriers: (1) lying between the cardiovascular generator and the recording device there is a series of still mysteriously complex springs and dampers in the elastic connections through which the forces must be transmitted; (2) the recording systems themselves are not ideal; and (3) most of the knowledge of the meaning of ballistocardiograms has been acquired from empirical clinical correlation and not from satisfactory physiologic experiments.

At the present time, three general types of ballistocardiographs are in common use: (1) the Starr high-frequency, undamped bed, (2) the low-frequency, critically damped bed of Nickerson and (3) the direct body pick-up developed by Dock. The latter, because of its lower cost and greater simplicity, is in widest use.

In order to unravel some of the mysteries of the mechanical behavior of the human body in response to the heart's impact upon it, Harrison and Talbot,[1] Burger et al.[2] and von Wittern[3] have recently analyzed current ballistocardiographic methods from both the theoretic and experimental standpoints. These analyses show that the three standard technics are all subject to influences that lead to distortion of the tracing and therefore to inaccuracy. For example, the contact between body and platform or floor allows oscillations of the body itself, which create distortions of the record entirely unrelated to the cardiovascular activity. From these studies has come the concept that in order to obtain maximal recording accuracy the body must be supported in such a way that there is the least possible constraint to oppose its motion. Several methods have been developed recently to approximate this condition and these have provided satisfactory records. Talbot et al.[4] accomplished this by floating the body on a very light raft in a pool of mercury, while Burger et al.[2] and von Wittern[3] did so by placing the body on a light suspended platform of very low natural frequency. The ballistocardiograms obtained by these newer systems are different from those recorded from the conventional systems. The question of whether they will be any more useful clinically must await the completion of investigations now in progress in several laboratories.

Conventional ballistocardiograms represent motions of the body in the head-foot direction but it seems clear that cardiovascular forces

* The opinions expressed here are those of a group working in ballistocardiography at the Johns Hopkins Hospital and School of Medicine consisting of: Drs. Benjamin M. Baker, Jr., Wm. R. Scarborough, Frank W. Davis, Jr., Robert E. Mason, Martin L. Singewald and Dennis C. Deuchar. Support for the work of this group is provided in part by a grant (H-327) from the National Heart Institute, National Institutes of Health, Public Health Service. Drs. Scarborough and Deuchar are Howard Hughes Fellows.

produce motions in other directions as well. Records of these motions have been obtained by a variety of technics.[5–9] Accumulated evidence indicates that such records may contain information not demonstrable in the usual head-foot record but, like the latter, the physiologic significance of these remains obscure.

In spite of the limitations just discussed, ballistocardiography has nevertheless aroused considerable interest, and rightly so. The fact that the record is in some way related to heart "strength" is established by the cadaver studies of Starr[10] which have provided the only real scientific data available on this point. Evidence for the validity of this concept is the fact that the records of young normal individuals, who it seems fair to assume have hearts of normal strength, are invariably normal. On the other hand, records from individuals with seriously weakened hearts are almost always abnormal. Furthermore, abnormal records from individuals with weakened hearts frequently become quite normal when the failure of these hearts is corrected by appropriate therapy. Perhaps even more pertinent to this type of reasoning is the observation that records of patients with angina pectoris may become grossly abnormal during attacks of ischemia only to improve promptly when the attack of ischemia has passed.

The assumptions that can be made from these empirical correlations are stimulating, but a solid physiologic foundation for the discipline is largely lacking. Progress in the field of electrocardiography over the years seems analogous. It took many years for such patterns as those of digitalis effect, electrolyte disturbance, ischemia and pericarditis to be accorded physiologic meaning. The technic was clearly an invaluable tool at all stages of its growth, but as long as the records it provided had to be related to clinical states and interpreted by memory, its practical value was small.

Many investigators have studied the ballistocardiograph intensively as a possible aid to the management of patients with coronary artery disease. This interest began when Starr[10] found the ballistocardiogram of patients with coronary artery disease frequently abnormal when all other tests of the circulation were normal.

The results of recent study of the role of ballistocardiography in the clinical management of patients with coronary disease thus far are not definitive.[11–15] Patients with clear-cut coronary artery disease usually but not always have ballistocardiograms abnormal in form. However, normal individuals who are comparable in age have been found to have a surprisingly high incidence of abnormal records. Until the physiologic meaning of these results is forthcoming or until long and careful clinical follow-up provide more and better information, opinion regarding the value of the technic should be guarded. At present, two tentative conclusions may be drawn: (1) abnormal ballistocardiograms are sufficiently uncommon in control subjects under the age of forty to make one suspicious that a young, presumably normal person with an abnormal record has myocardial disease; and (2) a normal record in older persons may perhaps be regarded with optimism, as many older persons show abnormal records even though they are normal by all other means of examination.

The two-step exercise test used in conjunction with the ballistocardiograph has, in the hands of some,[16] seemed of value in the separation of patients with coronary artery disease from normal controls. Others[17] have not been so enthusiastic about the value of this procedure. The only stress test that seems impressively to differentiate between normals and patients with coronary artery disease is one based on the ballistocardiographic effect of cigarette smoking. Dock[18] first observed changes in the ballistocardiogram after smoking. Henderson[19] and, more recently, Davis[17] utilized this procedure as a clinical test. Davis found that after cigarette smoking the ballistocardiograms of patients with coronary artery disease deteriorated nine times as often as did those of controls. He also observed that the ballistocardiographic alterations seen after smoking could be reproduced by the sublingual administration of nicotine. This test requires more documentation and study before its clinical value will be fully determined.

In the future, the clinical value of ballistocardiography will undoubtedly be more sharply defined by the results of long range follow-up studies now being conducted on subjects with and without cardiovascular disease. The chief hope for progress in this field, however, rests upon the belief that experimental work will ultimately allow a precise correlation between the details of the ballistocardiogram and the details of cardiovascular physiology and in so doing will provide us with a relatively simple clinical method for observing the dynamic performance

of the circulatory system. These physiologic studies must be complemented by others designed to improve instrumental methods.

Until more is known about this new and complex field, ballistocardiography should be considered a promising, though still experimental, method. A reasonable amount of healthy skepticism is recommended to the clinician who insists on employing the technic. He will do well to remember that the value of methods such as this are beyond dispute only when they measure known physiologic phenomena. The clinician should recognize the danger of making a diagnosis of coronary artery disease based solely on an abnormal ballistocardiogram until more is known of its significance. Iatrogenic cardiovascular neuroses are very difficult to correct.

A. McGehee Harvey, M.D.

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Clinical Studies

The Syndrome of Patent Ductus Arteriosus with Reversal of Flow*

DANIEL S. LUKAS, M.D., JORGE ARAUJO, M.D. *and* ISRAEL STEINBERG, M.D.
New York, New York

THE usual direction of blood flow through a patent ductus arteriosus is from aorta to pulmonary artery. Reversal of flow with shunting of blood from pulmonary artery to aorta of sufficient magnitude to give rise to cyanosis is a phenomenon that has been considered to occur either terminally or during cardiac failure.[2-4] During the past three years, however, we have observed four patients with patent ductus arteriosus who did not have congestive failure and who survived for many years after the onset of reversal of flow. The clinical and physiologic features presented by these patients and others reported recently are characteristic enough to deserve the designation of a syndrome.

Prior to 1953 there were available in the literature only five well documented and completely studied cases in which associated anomalies, particularly coarctation of the aorta, septal defects and patent foramen ovale, were conclusively excluded.[5-8] The recent reports of Dammann and co-workers and Hultgren et al. have added an additional seven.[9,10]

CASE REPORTS

CASE I. A twenty-six year old white secretary was admitted to The New York Hospital on April 30, 1951, for evaluation of a cardiac murmur known to be present since the age of three weeks. She was asymptomatic until the age of sixteen when easy fatigability and exertional dyspnea developed and became slowly progressive. She had never noted cyanosis.

Physical examination revealed a normally developed woman with pink finger nail beds and cyanotic, moderately clubbed toes. Blood pressure was 128/80 (right arm) and 140/80 mm. Hg (left leg). The heart was not enlarged to percussion. A long, harsh, systolic murmur, maximal

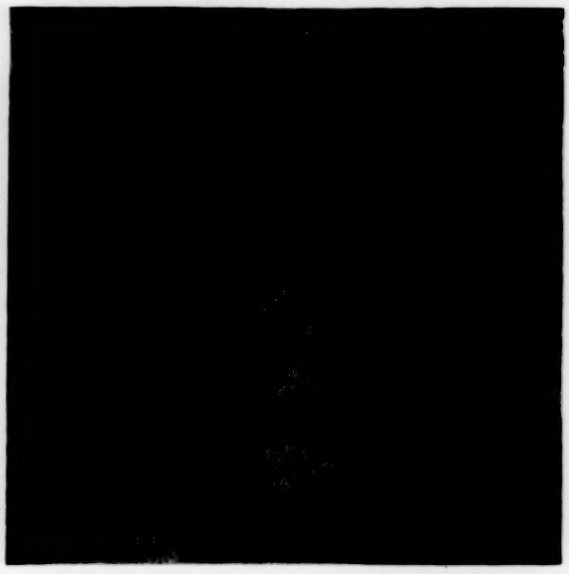

FIG. 1. Case I. Roentgenogram of the chest.

in the second left intercostal space, was heard along the upper left sternal border. A separate, blowing, high-pitched, diastolic murmur was present in the same area. The second pulmonic sound was accentuated and greater than the second aortic sound. No signs of cardiac failure were present.

Laboratory data were as follows: hemoglobin, 16 gm./100 cc.; erythrocytes, 8.5 m./cu. mm. The electrocardiogram showed normal sinus rhythm, peaking of the P-waves in leads II and III, right ventricular hypertrophy and vertical position of the heart. The intrinsicoid deflection

* From the Cardio-Pulmonary Laboratory and the Departments of Medicine and Radiology of The New York Hospital, Cornell Medical Center, New York, N. Y. Previously presented in part to The Eastern Section of the American Federation for Clinical Research, December 5, 1952, New York.[1] This work was supported by The New York Hospital, Cornell Medical Center Research Fund and The New York Heart Association.

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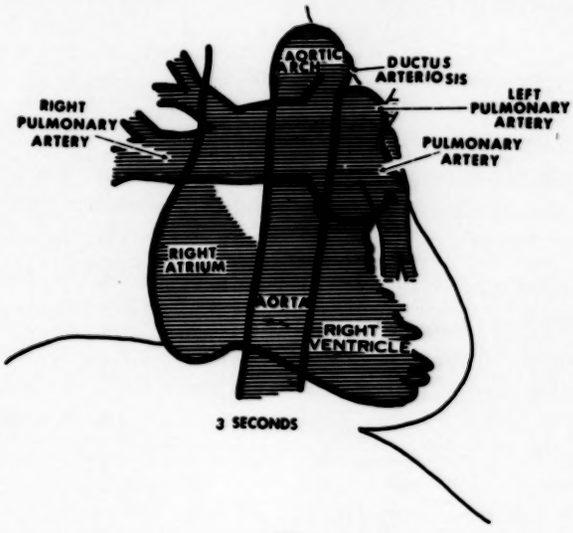


2B

FIG. 2. Case 1. A, angiocardiogram, frontal view, at 3 seconds demonstrating simultaneous opacification of the pulmonary artery, ductus and descending aorta. Note absence of contrast material in ascending aorta and brachiocephalic vessels; B, tracing of A.

was .04 second in V_1. R/S in V_1 was 15/0 mm. S_{V_6} was 9 mm. The R-T segments were displaced downward and T-waves were diphasic in V_{1-4}. Heart size in conventional roentgenograms and fluoroscopy of the chest was within normal limits. (Fig. 1.) The right ventricle was prominent and there was pronounced enlargement of the pulmonary artery and branches, the pulsations of which were moderately increased.

Angiocardiography (Fig. 2) demonstrated considerable enlargement of the right ventricle, main stem pulmonary artery and branches. Conclusive evidence of a ductus with reversal of flow was provided by opacification of a large patent ductus and the descending aorta at the time of filling of the pulmonary artery. Recirculation of contrast substance through the

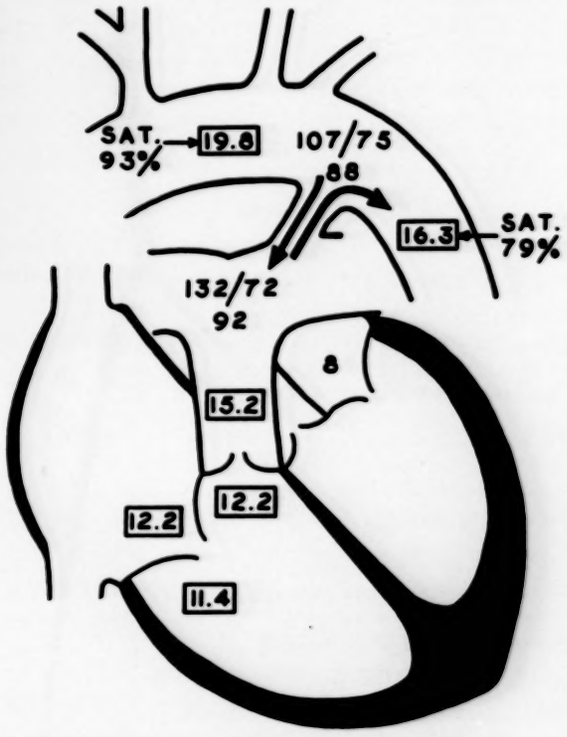


FIG. 3. Diagrammatic presentation of data obtained by cardiac catheterization in Case 1. Blood oxygen contents in volumes per cent are enclosed by rectangles; pressures (systolic/diastolic and mean) in mm. Hg are unenclosed; sat. equals oxyhemoglobin saturation in per cent.

pulmonary arteries after the left ventricle and ascending aorta had opacified indicated that a left to right shunt through the ductus was also present.

Cardiac catheterization (Table 1 and Fig. 3) revealed right ventricular and pulmonary arterial hypertension with a systolic pressure greater than systemic systolic. There was an increase of oxygen content of blood from the outflow tract of the right ventricle to the pulmonary artery of 3 vol. per cent. The oxyhemoglobin saturation of blood sampled from the right brachial artery was within normal limits whereas blood simultaneously obtained from the right femoral artery was unsaturated. The findings were diagnostic of patent ductus with bidirec-

tional shunting of blood. The 0.8 vol. per cent increase of blood oxygen from inflow to outflow tract of the ventricle was interpreted as indicating pulmonic insufficiency.

Surgical correction of the defect was attempted. During the operation a short ductus arteriosus, 2.5 cm. in diameter, was found. There was no associated coarctation of the aorta. Attempts to secure a ligature about the ductus resulted in excessive bleeding from its friable wall and the procedure had to be abandoned. Biopsy of the lung showed the small arteries to have thick hyaline walls. The media and intima of the medium sized arteries were markedly thickened.

Since discharge the patient has returned to her secretarial job. Her symptoms remain unchanged.

TABLE I

DATA OBTAINED BY CARDIAC CATHETERIZATION

		Case No.: I		II		III	
		Blood Oxygen Content (vol. %)	Pressures (mm. Hg) Systolic/ Diastolic (mean)	Blood Oxygen Content (vol. %)	Pressures (mm. Hg) Systolic/ Diastolic (mean)	Blood Oxygen Content (vol. %)	Pressures (mm. Hg) Systolic/ Diastolic (mean)
Brachial artery (right)		19.8	107/75 (88)	25.4	.....	27.6	.....
Femoral artery (right)		16.3	.....	17.2*	97/60 (69)*	24.0	117/70 (79)
Pulmonary artery		15.2	132/72 (92)	17.2	111/72 (77)	20.3	113/70 (92)
Right ventricle (outflow tract)		12.2	120/5	12.4	105/11	19.5	113/5
Right ventricle (inflow tract)		11.4	.....	12.6	.....	19.2	.....
Right atrium		12.2	(1)	14.6	(12)	19.1	(3)
Superior vena cava		14.2	.....	15.4	.....	20.6	.....
Oxyhemoglobin saturation, %	Brachial artery	93.3		94.0		94.1	
	Femoral artery	78.9		64.5		84.1	
Pulmonary blood flow, L./min./sq.M., B.S.A.		3.32		2.14		2.18	
Left-right shunt, L./min./sq.M., B.S.A.		1.31		0.79		0.47	
Body surface area (B.S.A.) in sq.M.		1.44		1.82		1.53	

* Obtained at end of procedure when rapid auricular fibrillation was present.

CASE II. A thirty-seven year old white, male, aluminum worker was advised from early childhood to restrict activity because of some cardiac abnormality. The patient had an asymptomatic and active childhood and adolescence and as an adult had been without significant cardiac embarrassment except for moderate exertional dyspnea. An attack of phlebothrombosis involving the left leg led to the discovery of polycythemia and cardiac murmurs. He was admitted for investigation of these abnormalities on June 10, 1952.

Physical examination disclosed a slightly obese, white male, appearing neither acutely nor chronically ill. There was definite cyanosis and clubbing of the toes; the lips and fingers were normally pink. Blood pressure was 130/90 mm. Hg (right arm) and 180/100 (left leg).

By percussion the heart was moderately enlarged to the left. A loud, rough, systolic murmur and a faint, short, diastolic murmur were heard in the pulmonic area. The second pulmonic sound was very accentuated. No signs of cardiac failure were present.

Laboratory data were as follows: hemoglobin, 22 gm./100 cc.; erythrocytes, 7.0 m./cu. mm.; hematocrit, 75 per cent. Circulation time (decholin®) was 16 seconds. The electrocardiogram showed normal sinus rhythm, marked clockwise rotation of the heart and evidence of right ventricular hypertrophy. R/S in V_1 was 2.5/2 mm. R was small and S deep in the remainder of the precordial leads. RT-T was coved from V_1 to V_4. Conventional roentgenograms of the chest revealed a moderately enlarged heart and prominence of the pulmonary artery and its branches. Some increase of pulmonary artery pulsations was noted during fluoroscopy.

During angiocardiography the sequence of opacification of the cardiac chambers and aorta was normal. There was no evidence of intracardiac or aortic-pulmonary shunt or coarctation of the aorta. The main stem pulmonary artery and branches were considerably enlarged. The caliber of the mid-ascending and transverse portions of the aorta was increased.

Cardiac catheterization (Table 1) revealed severe right ventricular and pulmonary arterial hypertension. Blood from the pulmonary artery contained 4.8 vol. per cent more oxygen than blood from the right ventricle. Most striking was the normal right brachial arterial blood oxyhemoglobin saturation and the marked unsaturation of the right femoral arterial blood. The latter sample was obtained at the end of the procedure after auricular fibrillation accompanied by increase in cyanosis of the toes had developed. The decrease of systemic arterial pressure that occurred with the arrythmia favored increased reversal of flow through the ductus. The rhythm reverted to normal after 1.6 mg. of lanatoside C.

At thoracotomy a patent ductus arteriosus, 4.0 cm. in diameter, was found. During the operation blood pressure fell progressively to 68/40 and cyanosis of the lower extremities became pronounced. Obliteration of the ductus with a tourniquet was followed by complete disappearance of the systemic blood pressure. Permanent ligation of the ductus was therefore not attempted.

Following an uneventful postoperative course the patient was discharged and followed in the outpatient department. One month postoperatively right ventricular failure with hepatomegaly and ankle edema developed and responded promptly to a regimen of digitalis, phlebotomy, mercurials and sodium restriction. On digitalis and monthly phlebotomies designed to maintain the hematocrit below 55 per cent his course has been very favorable. His only symptom is mild exertional dyspnea and he regards his activities as virtually unlimited.

Case III.* A twenty-two year old Iranian male student was admitted on March 9, 1952, with a history of progressive exertional dyspnea and fatigue since age two. During the eight years prior to hospitalization he had noticed cyanosis and clubbing of his toes. A chest x-ray taken at the age of seven was interpreted as showing "a collapsed left lung."

Physical examination revealed a short, white male who did not appear ill. Blood pressure was 120/74 (left arm) and 140/80 (right leg). Breath sounds were diminished over the left hemithorax, which was smaller than the right and expanded poorly. The heart was displaced to the left. Varying murmurs were heard over the heart. On one occasion a faint systolic murmur was heard in the second left interspace and in the interscapsular region. On another occasion, a presystolic and loud rumbling diastolic murmurs were heard in the left axilla. The finger nail beds appeared plethoric but not cyanotic; the toes were definitely clubbed and cyanotic.

Laboratory data were as follows: hemoglobin 21.7 gm./100 cc.; erythrocytes, 7.7 m./cu. mm.; hematocrit, 70 per cent. The electrocardiogram showed normal sinus rhythm, right axis deviation and changes consistent with marked clockwise rotation of the heart and right ventricular hypertrophy. The intrinsicoid deflection in V_1 was .05 second. R/S in V_1 was 17/0 mm. There was an rsR′ pattern in $V_{2,3}$. S_{V_6} was 20 mm. RT-T was depressed and coved from V_1 to V_5. Roentgenogram of the chest showed marked displacement of the heart and mediastinum to the left. Bronchography disclosed absence of the left main bronchus.

In the angiocardiogram a very dilated pulmonary artery, a short patent ductus arteriosus,

* This case has been reported in more detail previously.[11]

16 mm. in diameter, and the descending aorta were opacified simultaneously. The left pulmonary artery was absent. Persistent opacification of the pulmonary artery at time of filling of the left ventricle and ascending aorta suggested that a left-right shunt through the ductus also existed. The absence of the left pulmonary artery, left bronchus and the mediastinal displacement indicated that the left lung was congenitally absent.

The most significant data obtained by cardiac catheterization (Table 1) were marked pulmonary arterial hypertension, shunting of oxygenated blood into the pulmonary artery, normal oxyhemoglobin saturation of right brachial arterial blood and reduced saturation of right femoral arterial blood. These findings confirmed the bi-directional nature of the shunt through the ductus.

Following discharge from the hospital the patient returned to his student activities. He was last seen in July, 1952.

CASE IV. A twenty-four year old white female was admitted to The New York Hospital on November 24, 1952, for angiocardiographic studies. At age ten, a murmur typical of a patent ductus arteriosus was heard for the first time. At twelve, a febrile illness developed which subsided spontaneously in a few months and was thought to be possible rheumatic fever. Subsequently exertional dyspnea, easy fatigue and palpitations appeared and her heart murmur became inconstant. At times no murmur was audible. Progression in symptoms and marked anxiety over her cardiac ailment restricted her activity greatly. She had several admissions to other hospitals, the first in December, 1947.

During those admissions a rough systolic murmur was inconstantly heard in the pulmonic area. Faint cyanosis of the fingers was first noted in January, 1950, and subsequently became more severe. The patient observed that at times her left hand was more cyanotic than the right. Direct laryngoscopy had revealed paralysis of the left vocal cord. Polycythemia had been present since December, 1947. In February, 1950, brachial arterial blood oxyhemoglobin saturation was found to be 92 per cent. Femoral arterial blood obtained a few days later at the time of cardiac catheterization had a saturation of 79 per cent. Cardiac catheterization had been performed on three separate occasions and failed to reveal any evidence of left-right shunt. The pulmonary arterial pressure was 107/70.

Physical examination revealed a well developed, anxious and emotionally immature white female. The buccal mucous membranes and all nail beds were cyanotic, the fingers of the right hand less than the left. Clubbing was absent. The heart was not enlarged. The second pulmonic sound was very accentuated and greater than the second aortic sound. Along the left sternal border, loudest in the third and fourth intercostal spaces, was a harsh, low-pitched, systolic murmur. A systolic thrill was present in the same area. A non-tender liver edge was felt at two fingerbreadths below the right costal margin. There was no edema or venous distention. Blood pressure was 92/80 mm. Hg (right arm) and 94/84 (left arm).

Laboratory data were as follows: hemoglobin, 21.0 gm.; erythrocytes, 8.0 m./cu. mm.; hematocrit, 63 per cent. The electrocardiogram revealed normal sinus rhythm, right ventricular hypertrophy and right axis deviation. The intrinsicoid deflection in V_1 measured .04 second. R/S in V_1 was 8/2 mm. $RS_{V_{2-4}}$ were equiphasic. In the roentgenogram of the chest the transverse cardiac diameter was normal. The pulmonary artery and its branches were very large.

Angiocardiography (Fig. 4), performed under anesthesia because of the emotional state of the patient, disclosed simultaneous opacification of the pulmonary artery, a patent ductus 1.2 cm. in diameter, and the descending aorta. Some of the contrast substance entering the aorta from the pulmonary artery was observed to spread in retrograde fashion up into the brachiocephalic arteries, more so on the left than the right. Samples of blood obtained at time of angiocardiography revealed an oxyhemoglobin saturation of 73 per cent in the right radial artery and 56 per cent in the right femoral artery.

The patient returned to her parent hospital where several months later an attempt was made to ligate the ductus. Progressive deterioration of her cardiovascular status developing during the course of the operation was not reversed by ligation of the ductus and she expired.

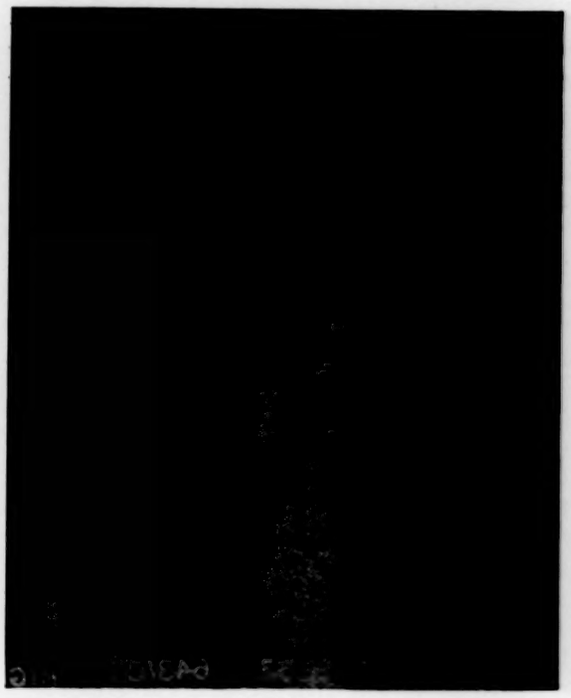
DISCUSSION

PHYSIOLOGIC CONSIDERATIONS. Several hemodynamic alterations are common to our patients. One of these is elevation of the pulmonary

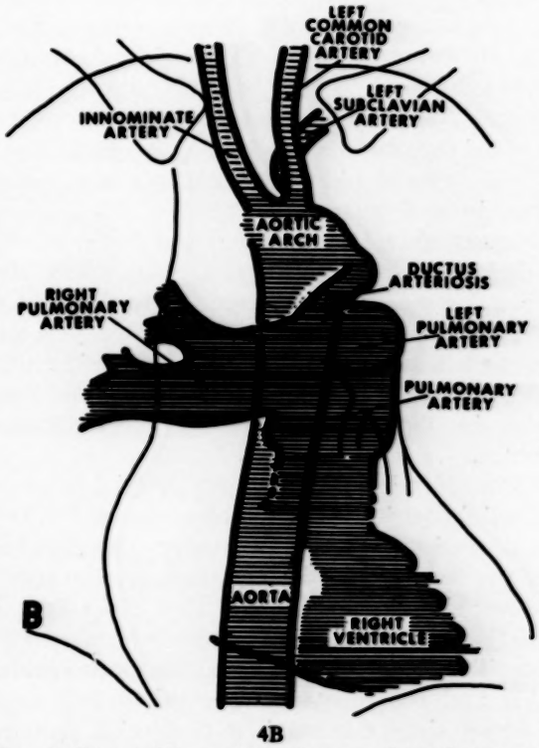
arterial pressure to a level greater than the systemic arterial pressure. This pressure difference, as in the previously reported cases, was not large and was usually greatest during systole. During diastole a pressure difference either could not be demonstrated or a gradient from aorta to pulmonary artery was present. It is of importance that the pressure differences were somewhat variable from one cardiac cycle to another. Since the phasic alterations in peripheral arterial pressure are not precisely equivalent to similar alterations in aortic pressure, it is not possible to analyze the pressure gradients minutely.

As a consequence of a pressure gradient from pulmonary artery to aorta, unsaturated pulmonary arterial blood is shunted into the aorta. Since the patent ductus inserts into the aorta below the origin of the left subclavian artery, this blood is swept down the descending aorta and into its branches. (Fig. 3.) The arterial oxyhemoglobin saturation of the arterial blood supplying the head and upper extremities is therefore higher than in the trunk and lower limbs. In three of our cases and in five of the nine cases from the literature in which simultaneous brachial and femoral arterial blood samples were obtained brachial arterial saturation was above 91 per cent whereas femoral arterial blood was distinctly unsaturated.[5,8–10] This observation indicates that little or none of the venous shunt entered the brachiocephalic arteries.

In Case IV retrograde spread of the venous shunt into the aortic arch and arterial trunks arising therefrom was clearly demonstrated in the angiocardiogram (Fig. 4) and by the very low saturation of the right radial arterial blood. In seven of the cases in the literature similar retrograde spread of the shunt into the vessels of the head and upper extremities was observed.[6–10] The amount of this spread was variable as indicated by brachial arterial oxyhemoglobin saturations of 59 to 86 per cent. In one of their cases Bothwell et al.[8] were able to demonstrate by ear oximetry that part of the shunted blood entered the left carotid but not the right innominate artery. During exercise the arterial saturation in the right ear was 93 per cent and 84 per cent in the left ear. The preferential distribution of the retrogradely directed portion of the shunt into the arteries closest to the ductus (i.e., the left brachial and left common carotid arteries [Fig. 4]) was similarly indicated



4A



4B

FIG. 4. Case IV. A, angiocardiogram, frontal view, at 2.5 seconds demonstrating shunting of contrast material from pulmonary artery to aorta via the patent ductus. Note retrograde spread of shunt into the brachiocephalic arteries; B, tracing of A.

in our Case IV and one of the cases of Dammann et al.[9] by deeper cyanosis of the left than the right hand. Despite retrograde spread of the venous shunt into the aortic arch the femoral arterial oxyhemoglobin saturation in all adequately documented cases was lower than the simultaneously determined brachial saturation. The smallest difference between saturations was 8.4 per cent.[8]

Reliable calculation of the magnitude of the right-left shunt and the systemic blood flow in patients with reversal of ductus flow is not possible. This is so because the fraction of systemic blood flow that supplies the head and upper extremities as compared to the trunk and lower extremities cannot be determined in a given patient. The abnormally large arteriovenous oxygen differences developed in both the upper and lower portions of the body (Table I) clearly indicate that systemic blood flow is subnormal. Accordingly the right-left shunt cannot be large.

In three of our patients the catheterization data demonstrated a coexisting left-right shunt through the ductus. The size of the shunts was small but comprised 14–39 per cent of the pulmonary blood flow which, like the systemic flow, was also subnormal. In six of nine previously reported cases in which adequate data bearing on this point are available, left-right shunting of blood through the ductus was also present.[5,8,9] The subnormal pulmonary and systemic blood flows in patients with reversal of ductus flow contrasts sharply with the greatly increased pulmonary flow and normal to slightly decreased systemic flow present in the usual patient with patent ductus. This implies that the over-all hemodynamic status is considerably poorer in the patient with reversal of flow than in the patient with an uncomplicated ductus.

The elevation of pulmonary arterial pressure is mainly attributable to a pronounced increase in the resistance of the pulmonary vascular bed to the flow of blood. It cannot be due to an increased pulmonary blood flow since flow is less than normal. In our first patient pulmonary "capillary" pressure (8 mm. Hg) was obtainable and the resistance was calculated to be fourteen times normal. The conclusion that the resistance was greatly increased in the other patients is inescapable even if very high values for pulmonary "capillary" pressure are assumed.

In view of the relatively fixed nature of the pulmonary vascular resistance and the variability of the systemic vascular resistance it can be anticipated that the amount of blood shunting in either direction through the ductus is variable in the same patient. Thus situations provoking a fall in systemic resistance will favor flow from pulmonary artery to aorta; conversely reversal of flow will be diminished and left to right flow promoted by increases in the systemic resistance This variable interrelation between systemic and pulmonary resistances explains the fall in arterial saturation and increase of cyanosis during exercise, excitement, anesthesia, all of which are associated with decrease in systemic resistance. It is probably partially responsible for the variations in the clinical picture from patient to patient with this syndrome.

CLINICAL FEATURES. The age range of our patients included with those reported prior to this paper was sixteen to forty-two years. There were eleven females and five males.

Easy fatigue and exertional dyspnea, slowly progressive over many years, are the outstanding symptoms. These symptoms do not curtail physical activity greatly but three of the patients in the literature were seriously handicapped.[5,9] The fatigue is readily explained by anoxia of the muscles of the trunk and lower extremities consequent to the anoxemia and low rate of blood flow. Although many factors may be implicated in the pathogenesis of the dyspnea, this symptom cannot be explained readily on the basis of our present knowledge of pulmonary physiology. Perhaps anoxia and fatigue of the respiratory muscles are responsible.

Cyanosis had not been present since birth in any of our patients. Its earliest onset was at age eight in Case III. In four of the cases in the literature it had been present since birth or early childhood.[7,9,10]

The peculiar and remarkable distribution of cyanosis in all our cases suggested the correct diagnosis prior to cardiac catheterization and angiocardiography. In three the toes were distinctly cyanotic while the fingers were normal although somewhat plethoric in appearance. In Case IV, the patient with reflux of the venous shunt into the aortic arch, all four extremities were cyanotic but the right hand least of all.

Unfortunately, information regarding the distribution of cyanosis in the reported cases is scanty; little attention appears to have been given to this very important clinical sign. In only three[6,8,9] was cyanosis of the toes noted to

be more pronounced than in the fingers. In one of these the left hand was more cyanotic than the right.[9]

Clubbing of the toes but not of the fingers was present in three of our patients and was entirely absent in one (Case IV). In the literature clubbing of all digits is described in three cases[9,10] and of the toes but not the fingers in one.[10] Clubbing, like the cyanosis, is related to the distribution of the right-left shunt.

Murmurs. The typical continuous machinery murmur of a patent ductus was not present in any of our cases or those in the literature. Most frequently heard was a harsh and loud, but occasionally soft, systolic murmur in the third and fourth intercostal spaces along the left sternal border. A coexisting but distinctly separate, high-pitched, decrescendo diastolic murmur was heard in the pulmonic area and down the left sternal border in two of our patients and in four of the reported cases.[8,9] The murmurs were occasionally variable from time to time and on occasions, as in one of our patients, were absent. Absence of murmurs was a notable feature of one of the cases of Hultgren et al.[10] The pulmonic second sound was invariably accentuated.

The altered dynamics of blood flow through the ductus explains the absence of a continuous murmur. The systolic murmur may be due to flow through the ductus during systole (when the pulmonary arterial-aortic pressure gradient is greatest) or to turbulent flow in the large pulmonary artery. The diastolic murmur is most likely due to pulmonic insufficiency consequent to the enlargement of the main pulmonary artery and the pulmonary hypertension. The murmur has all the auscultatory characteristics of pulmonic insufficiency.

Heart size was, in general, only slightly increased. Conventional roentgenography and especially angiocardiography revealed the enlargement to be mainly of the right ventricle. The main pulmonary artery and its branches were quite prominent. Pulsations of the pulmonary arteries were vigorous but in only one instance[5] were they of sufficient magnitude to be called hilar dance.

Polycythemia was a prominent feature of all our cases and nine of the reported cases. Since most of the erythrogenic marrow is supplied by blood from the descending aorta it is not surprising that polycythemia was as severe in the patients with normal brachial arterial oxygen saturation as in those with more general distribution of the right-left shunt.

At first glance it would appear that a patient whose right-left ductus shunt is distributed mainly into the descending aorta is an excellent subject for study of the effects of localized anoxemia on the bone marrow. In Case II, marrow was obtained simultaneously from the tip of the left clavicle and the right iliac crest. Both specimens showed an equal and slight degree of erythroid hyperplasia. No conclusions could be drawn from the study since it was impossible to rule out retrograde spread of the venous shunt to the head and arms during the daily activities of the patient by mechanisms discussed in the physiologic section.

Electrocardiograms showed a pattern of right ventricular hypertrophy in our cases and in all those from the literature. Right axis deviation was likewise present except in Case II and in one of the cases reported by Bothwell et al.[8] These findings are particularly significant since electrocardiographic evidence of right ventricular hypertrophy is rare in patent ductus arteriosus and is found only in those cases complicated by considerable right ventricular hypertension.[12]

The electrocardiographic pattern in three of our patients was that of systolic rather than diastolic overloading of the right ventricle.[13]

Angiocardiography is a valuable diagnostic tool in patent ductus with reversal of flow. In three of our cases simultaneous opacification of the pulmonary artery, ductus and descending aorta by the contrast material provided vivid proof of the diagnosis. The study was of particular importance in Case IV, in which cyanosis of the upper as well as lower extremities was present and in which extensive clinical study and several cardiac catheterizations had failed to establish the diagnosis. Angiocardiography was similarly diagnostic in five of the six previously reported cases. Failure in one, as well as in one of ours, may have been due to absence of reversal of flow at time of study.

For purposes of differential diagnosis, angiocardiography is very valuable, especially in patients with generalized cyanosis who are frequently misdiagnosed as Eisenmenger's complex. In such patients the study aids in ruling out the presence of other lesions producing a venous shunt, in particular over-riding of the aorta, patent foramen ovale associated with pulmonary hypertension, and aortic septal defect with reversal of flow. It is also a reliable

method for excluding the presence of a co-existing coarctation of the aorta with insertion of the ductus distal to the point of coarctation for in this combination of lesions differential cyanosis between the upper and lower portions of the body may be present if a significant portion of pulmonary vascular bed. This change appears to be related to extensive anatomic alterations in the medium- and small-sized pulmonary arteries. Lung biopsy in Case 1 and autopsy of four of the patients in the literature revealed the walls of these vessels to be thickened and the lumina

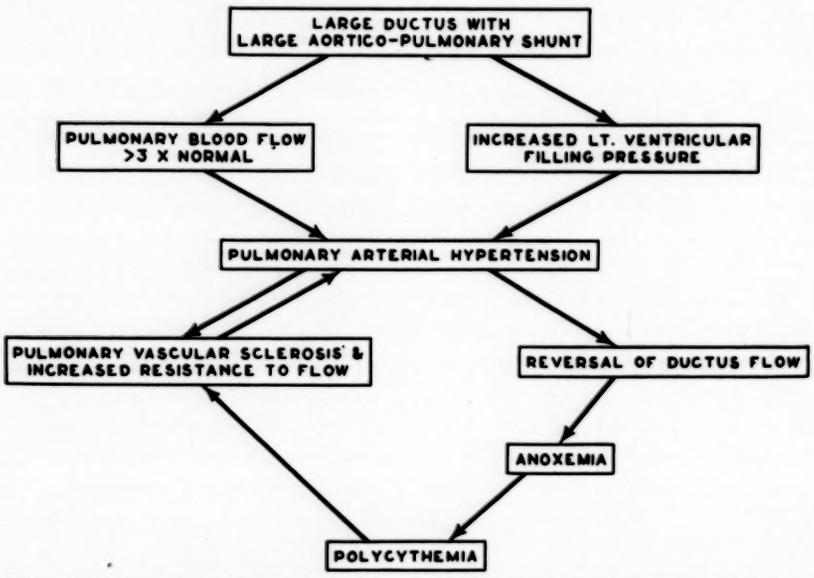


FIG. 5. Schema of pathogenesis of reversal of flow in patent ductus arteriosus.

blood supplying the aorta is derived from the ductus.[6,14] Since there may be little or no difference between the blood pressures in the femoral and brachial arteries[14] angiocardiography may be the only means of detecting the coarctation.

Cardiac catheterization, as indicated in the section on physiologic considerations, frequently reveals the diagnosis, is of aid in excluding coexisting anomalies and provides information useful in deciding about therapy. A pulmonary arterial pressure in the range of systemic pressure, femoral arterial oxyhemoglobin saturation lower than simultaneously obtained brachial saturation and evidence of a left-right shunt into the pulmonary artery comprise the diagnostic triad. Evidence of left-right flow through the ductus, however, is not obtainable in all cases. It may be necessary to exercise the patient, or otherwise induce a decrease in systemic vascular resistance, in order to promote reversal of flow and demonstrate the difference in arterial saturation between the upper and lower portions of the body.

PATHOGENESIS

Reversal of ductus flow could not occur without a great increase of the flow resistance of the narrowed by hypertrophy of the muscular coat and proliferation of the intima.[5,6,9] Another striking feature was the presence of multiple thrombi, many recanalized, in the medium-sized arteries. In Campbell's case,[15] not included in this report because there was an associated patent foramen ovale, the only occlusive alterations were multiple, organized and recanalized thrombi widely distributed throughout the pulmonary arteries.

The mode of pathogenesis of the vascular lesions is not known. Our concept of their development and the role they play in production of reversal of flow is diagrammed in Figure 5. We believe it is significant that our patients had unusually large ducti, which early in the course of the disease probably transmitted very large flows from aorta to pulmonary artery. Ductus diameters were 1.2, 1.6, 2.5 and 4.0 cm. and in the literature are reported as 1.0, 1.5 cm., "large" and "huge."[5,8,9]

Most patients with patent ductus have normal or only slightly elevated pulmonary arterial pressures because the normal pulmonary vascular bed can accommodate increase in blood flow up to three times normal without increase in pressure.[16,17] Ducti large enough to produce

pulmonary flows greater than three times normal are frequently associated with pulmonary arterial hypertension even though the pulmonary vascular resistance is normal.[18,19] The hypertension is of moderate grade and is due not only to a flow greater than the vessels can accommodate but also to a "back pressure" effect from the overworked left ventricle, as indicated by increase of the pulmonary "capillary" pressure (equivalent to left atrial and pulmonary venous pressure).[18]

Once established, chronic pulmonary arterial hypertension may lead to the development of pulmonary arteriosclerosis as appears to be the case in mitral stenosis.[20,21] With progressive restriction of the pulmonary vessels pulmonary arterial pressure increases. The hypertension at this stage in the development of the disease, in contrast to the early phase, is less due to augmented pulmonary blood flow than to the alterations in the pulmonary vessels. Indeed, because of the diminution in aortic-pulmonary arterial pressure gradient, ductus flow is relatively small and may occur only during systole.[22,23] With further increase of pressure reversal of ductus flow occurs.

Polycythemia secondary to the venous shunt exerts several deleterious effects on pulmonary hemodynamics. Because of its effect on blood viscosity it aggravates the resistance to the flow of blood through the lungs, thereby accentuating the pulmonary hypertension.[24] Also it favors the development of thromboses, to which the sclerotic pulmonary arteries appear particularly vulnerable. Reversal of ductus flow, therefore, is the first segment of a vicious cycle which favors the perpetuation and progression of the reversal and in which polycythemia appears to play an important role. (Fig. 5.)

The pathogenetic schema described probably does not apply completely to patients with reversal of flow from birth or early infancy, as in four of the previously reported group.[7,9,10] In these the pulmonary vascular bed may be congenitally abnormal as in primary pulmonary hypertension and Eisenmenger's complex. It has been suggested that the vascular defect in these diseases consists of failure of the vessels to transform from their fetal form.[25] Later in years, however, arteriosclerosis and thromboses are superimposed.

Anoxia, which constricts the pulmonary arterioles, has been cited as a possible cause of the increased pulmonary vascular resistance.[9] Constriction, however, has been demonstrated to occur only when the oxygen concentration of the alveolar air bathing the pulmonary vessels is distinctly subnormal.[26,27] It has not been demonstrated to occur as the result of a central veno-arterial shunt or peripheral anoxia. That a low alveolar oxygen concentration was not present in our patients is indicated by the relatively normal brachial arterial oxyhemoglobin saturations in three. A low alveolar oxygen tension may contribute to the development of pulmonary hypertension in patent ductus at altitudes or if emphsema coexists. In the autopsied cases the lungs were normal aside from the vascular lesions. The effects of a low alveolar oxygen tension on the pulmonary arterioles and on the development of polycythemia may explain why pulmonary hypertension in patent ductus appears to be more frequent in communities located at considerable altitude above sea level, such as Mexico City.[28]

TREATMENT

It is now agreed that the ideal treatment of all patients with patent ductus is surgical obliteration of the ductus.[2] There is considerably less agreement about surgery in patients with reversal of flow.[2,9,10,12] The surgical risk and difficulties involved and disagreement over the physiologic soundness of closing the ductus are the main aspects of the problem.

It is well known that patients with severe pulmonary arterial hypertension are poor surgical risks because of their hemodynamic status and the large size of their ducti. Thus Crafoord reports eight surgical deaths among sixteen patients with patent ductus complicated by pulmonary hypertension but without reversal of flow.[29]

Some difficulties were encountered during attempts to close the ducti of all patients with reversal. In Case I, the large ductus was so friable and under so much pressure that it bled excessively when manipulated. In the case of Novelo and associates death occurred when a rent developed in the wall of the atherosclerotic pulmonary artery after a ligature was placed about the ductus.[7] The poor tolerance for anesthesia and open chest surgery is demonstrated by Cases II and IV, both of whom developed hypotension during the course of the operation.

It has been contended that the ductus in this syndrome acts as a safety valve which, by buffering the quantity of blood flow through the lungs,

prevents the pulmonary arterial pressure from rising to higher levels.[9,10] If the ductus is ligated the additional flow through the lungs and concomitant increase of pressure required to propel it would cause failure of the right ventricle. Thus death in the case of Pritchard et al. occurred apparently of right ventricular failure eight hours after ligation.[6] Another case (not reviewed here) died of acute cor pulmonale two days after ligation.[12] Among the patients reviewed here five came to operation and four died either of immediate operative complication, of some postoperative development or of right ventricular failure.[5,9] Among our four three were operated upon; the ductus could not be closed in two and the third died during the operation.

Some of the surgical experiences, however, are encouraging. One of the cases of Bothwell and associates had a partial ligation of the ductus with clinical improvement and the appearance of a continuous murmur two months later.[8] The Institute of Cardiology of Mexico reported three cases with intermittent reversal of flow in which marked decrease in pulmonary arterial pressure occurred after ductus ligation.[12] Pressures preoperatively were 104/63, 103/57 and 109/68 mm. Hg and fell to 32/11, 59/30 and 51/11 at two and a half, eleven and two months postoperatively. Such data indicate that at least in some cases the increased resistance of the pulmonary vascular bed is partially reversible. Similarly we have learned that the increased pulmonary vascular resistance commonly associated with mitral stenosis is decreased after mitral valvuloplasty.[30,31]

The concept that the ductus is a safety valve neglects the fact that the shunt is bidirectional in most cases. As long as any left-right shunt remains it is a contributing factor to maintenance of the pulmonary hypertension. Moreover the concept disregards the fact that reversal may or may not be present depending on the size of the systemic resistance relative to the pulmonary resistance. Thus a patient with severe pulmonary hypertension may not demonstrate cyanosis at rest (under which condition most studies are performed) and he will be considered to be a suitable candidate for ductus ligation even though reversal of flow that escapes the attention of the clinician develops during exercise.

It is reasonable to conclude that ligation of the ductus, though dangerous, may result in considerable benefit to patients with intermittent reversal or bidirectional shunt, particularly if they are young. Indeed, it is the only hope of halting the inevitable progression of pulmonary vascular disease and concomitant increase of right-left shunt. In those with no evidence of left-right shunt beneficial effects after ligation seem unlikely.

It has been suggested that at operation occlusion of the ductus be graded over a period of time to allow for cardiovascular adjustments to occur.[12] Partial ligation, as performed in Bothwell's case,[8] is dangerous because of possible rupture of the ductus. However, a two-stage procedure with partial ligation during the first and complete ligation during the second is a possible approach.

Conservative management is not altogether fruitless. Because of the role of polycythemia in the pathogenesis and aggravation of the syndrome, the hematocrit should be maintained at normal levels by periodic phlebotomy. Right ventricular failure, if it supervenes, does not necessarily herald the death of the patient. One of the cases of Dammann et al. responded well to treatment of several bouts of failure.[9] As indicated by the experience with our second case (the patient with the ductus of 4 cm. diameter), digitalis, mercurials and phlebotomy were effective in controlling failure and on a regimen of digitalis and monthly phlebotomies the patient has amazingly few symptoms.

SUMMARY

The physiologic and clinical features of four cases of patent ductus arteriosus with reversal of flow presented here and twelve cases selected from the literature are characteristic enough to warrant the designation of a syndrome. Pulmonary arterial hypertension of sufficient magnitude to cause shunting of venous blood from the pulmonary artery into the aorta (mainly the descending portion) is the physiologic basis of the condition. The hypertension is related to extensive arteriosclerotic and thrombotic alterations in the pulmonary vessels.

The usual clinical characteristics of uncomplicated patent ductus are absent. The continuous murmur is not heard and the pulmonary blood flow is small. Because of the distribution of the venous shunt there is cyanosis and clubbing of the toes and absent or less pronounced cyanosis and clubbing of the fingers. Right ventricular hypertrophy is present in both the roentgenogram and electrocardiogram. These findings permit the diagnosis to be made clinically.

Angiocardiography and cardiac catheterization establish the diagnosis unequivocally, are of aid in excluding coexisting defects and provide information needed in decision concerning ligation of the ductus. The surgical experience is limited but indicates that ligation of the ductus is hazardous but may be followed by considerable decrease in the hypertension.

The mode of pathogenesis of the pulmonary vascular lesions is not known but a large ductus capable of transmitting a very large left-right shunt early in the course of the disease is an essential factor. Polycythemia accentuates the venous shunt once it is established.

Patients with this syndrome are not necessarily in cardiac failure and may live for many years after its onset.

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Pulmonary Stenosis with Left to Right Shunt*

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THE recent literature has dealt extensively with the syndrome of congenital pulmonary stenosis associated with a right to left interatrial shunt.[1-6] Under such names as pulmonary stenosis with patent foramen ovale,[1,3,5] pulmonary stenosis with reversed interatrial shunt and the tetralogy of Fallot,[6] the clinical, pathologic and hemodynamic features have been described and the entity firmly established as the second most common variety of cyanotic congenital heart disease.

Simple or isolated pulmonary stenosis without intracardiac communications has also received much attention,[4,7-10] and has been shown on the one hand to be a mild condition of benign prognosis and on the other to be clinically and dynamically as severe as the cyanotic cases. It has been stressed that in the absence of septal defects "central" cyanosis does not occur.

Abrahams and Wood[4] have recently clearly described a third group of cases characterized by congenital pulmonary stenosis with a normal aortic root but complicated by intracardiac communications through which an over-all arteriovenous or left to right shunt occurs. Only a few other reports of this syndrome have been made[11,12] and it is the purpose of this communication to describe the clinical and hemodynamic findings in a similar group of patients and to discuss the implications of the syndrome.

The material comprises fourteen cases, all of which have been studied clinically and with the aid of cardiac catheterization. The cases may be classified basically as congenital pulmonary stenosis with normal aortic root according to Abrahams and Wood.[4] These authors subdivided their cases according to the site of the arteriovenous shunt but no allowance was made for the association of pulmonary stenosis and transposed pulmonary veins. Two such cases have been encountered in the present series and accordingly the following classification is suggested:

Pulmonary stenosis with left to right shunt:

1. Pulmonary stenosis with atrial septal defect
   (P.S. + A.S.D., eight cases)
2. Pulmonary stenosis with transposed pulmonary veins
   (P.S. + T.P.V., two cases)
3. Pulmonary stenosis with ventricular septal defect
   (P.S. + V.S.D., four cases)
4. Pulmonary stenosis with patent ductus arteriosus
   (P.S. + P.D.A., no example)

The salient clinical features of the cases are shown in Table I and are considered in detail in the discussion. Cardiac catheterization was carried out in the usual manner. Intracardiac pressures were measured with strain gauge manometers and photographically recorded. Blood oxygen determinations were carried out by the Van Slyke technic and arterial samples were drawn through inlying femoral or brachial needles. Oxygen consumption was obtained by the use of a Wet Test Meter and a Pauling Analyzer. Normal findings have been discussed in an earlier communication.[13] The results are summarized in Table II.

CASE REPORTS

CASE I. J. C. was a Caucasian male, aged twenty-eight, in whom a heart murmur was detected at the age of five when he was under

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treatment for pneumonia and empyema. During childhood his activities were restricted and he took no part in active sports. At present he complains of mild breathlessness on mounting a flight of stairs. He was rejected by the Armed Forces in World War II because of the heart murmur.

On physical examination the patient was well developed and well nourished. No cyanosis or finger clubbing was present. The blood pressure was 120/80 mm. Hg. The venous pressure and pulse were normal. The radial pulse was regular and of normal volume. The cardiac apex beat was normal in site and quality. There were no abnormal pulsations over the heart but a faint systolic thrill was palpated over the second left intercostal space. The heart sounds were audible in all areas, with the second sound loudest in the pulmonary area. A grade IV systolic murmur[14] was heard with maximal intensity at the site of the thrill, but well transmitted to the left axilla, the upper chest and neck.

An electrocardiogram showed a right bundle branch block pattern with a tall secondary R wave interpreted as due to right ventricular hypertrophy.[15]

Roentgenograms showed no cardiac enlargement but a marked prominence of the pulmonary artery segment and hilar vascular markings were noted. Vigorous pulsation of the left pulmonary artery was seen under the fluoroscope. (Fig. 1.)

Comment. The physical signs and electrocardiogram were compatible with the diagnosis of simple pulmonary stenosis but the radiologist concluded his report by suggesting the presence

TABLE I

CLINICAL FEATURES

	Case No.	Patient Age and Sex	Symptoms	Cardiac Enlargement	Precordial Heave	Thrill	Murmur	Second Sound	Electrocardiogram	Roentgenogram
1. Pulmonary stenosis and atrial septal defect	I	J. C., 28 M	Slight dyspnea on effort	0	0	+ 2LICS	S-IV 2LICS	P2+	RBBB‡ Tall R'V1♯	PA†† Vascularity + LPA pulsatile§§
	II	R. L., 16 F	0	0	3LICS*	+ 2LICS	2-IV 2LICS	P2+ split	RVH** and incomplete RBBB	PA+ Vascularity normal
	III	J. M., 10 M	0	0	0	0	S-III 3LICS	A2>P2	RVH Prolong.PR	PA+ Vascularity+
	IV	J. Mc., 28 F	Slight dyspnea on effort	0	0	+ 2LICS	S-IV 2LICS	A2>P2	Incomplete RBBB	Normal
	V	T. R., 28 F	0 — attack paroxysmal tachycardia 1 yr. ago	0	0	+ 3LICS	S-III† 3LICS	P2 dimin.	RVH	Slight gen. enlarg. PA+ Vascularity+
	VI	R. La., 30 M	0	0	0	+ 2.3.LICS	S-IV 2.3.LICS	P2 dimin.	RVH and incomplete RBBB Prolong.PR	PA+ Vascularity+
	VII	A. A., 11 M	0	0	0	+ 2.3.LICS	S-IV 2LICS	P2 dimin.	RVH	PA+
	VIII	L. S., 3 M	Attacks dyspnea and cyanosis on effort	0	0	+ 3LICS	2-IV 3LICS	P2>A2	RVH	Normal for age
2. Pulmonary stenosis and transposed pulmonary veins	IX	L. M., 11 M	Slight dyspnea tires easily	0	0	+ 2.3.LICS	S-IV 2LICS	P2 dimin.	RVH	PA+ Vascularity normal
	X	G. I., 3½ M	0	0	0	0	SIII 2LICS	P2 normal	RVH	Normal for age
3. Pulmonary stenosis and ventricular septal defect	XI	R. W., 18 M	0	0	0	0	S-III 2LICS	P2>A2	Normal Vertical position	PA+ Vascularity normal
	XII	S. M., 12 F	Slight dyspnea, tires easily	+	+ 2.3.LICS	+ 3LICS	S-IV-V 3,4,LICS ? EDM§	P2 normal	RVH	Slight gen. enlarg. PA+ Vascularity+ PA branches pulsatile
	XIII	D. K., 13 F	Slight dyspnea, cyanosis on effort	0	0	+ 2.3.LICS	S-IV 2-3-4 LICS	P2 elev.	RVH	PA+ Vascularity normal
	XIV	P. G., 10 F	Slight dyspnea on effort	+	+ 3.4.LICS	2.3.LICS	S-V 3LICS	P2 normal	RVH and possible incomplete RBBB	Slight enlarg. P+ Vascularity normal

* LICS—Left intercostal space adjacent to sternum.
† 2-III—Systolic murmur grade III.
‡ RBBB—Right bundle branch block.
§ EDM—Early diastolic murmur.
** RVH—Right ventricular hypertrophy.
†† PA—Pulmonary artery.
♯ R'V1—R prime in V1.
§§ LPA—Left pulmonary artery.

of a patent ductus arteriosus or other left to right shunt. Cardiac catheterization readily demonstrated a valvular pulmonary stenosis and in addition showed evidence of a left to right shunt at atrial level with a considerable excess of pulmonary over systemic blood flow. Subsequent to cardiac catheterization a successful Brock type valvulotomy was performed. The atrial defect was not explored at surgery.

TABLE II

RESULTS OF CARDIAC CATHETERIZATION

	Case No.	Patient, Age and Sex	Pressure (mm. Hg)					Oxygen Content (Vol. %)						Oxygen Saturation (%)		Blood Flow
			RA	LA	RV	PA	RV-PA Systolic Gradient	SVC	RA	RV	PA	LA	FA	LA	FA	Systemic: Pulmonary Ratio
1. Pulmonary stenosis and atrial septal defect	I	J. C., 28 M	2	...	90/7	27/9	63	12.3	19.9	19.2	19.5	....	20.2	.....	92	1:3.5
	II	R. L., 16 F	2	3	35/0	20/4	15	11.9	16.2	15.5	14.8	.....	16.8	.....	93	1:2
	III	J. M., 10 M	2	...	28/0	17.7	11	14.0	17.1	16.4	16.4	.....	17.4	.....	92	.....
	IV	J. Mc., 28 F	5	6.5	45/5	18/10	27	13.8	15.0	15.8	15.0	17.1	17.2	86	87	.....
	V	T. R., 28 F	3	...	45/0	30/9	15	10.8	13.2	13.9	13.4	.....	14.6	.....	90	1:2
	VI	R. La., 30 M	4	6	43/0	22/5	21	12.1	16.6	16.1	15.6	17 2	18.0	94	96	.....
	VII	A. A., 11 M	2	2	60/0	16/7	44	13.3	14.7	14.7	14.9	16.8	17.2	95	96	2:3
	VIII	L. S., 3 M	2	4	75/2	20/3	55	12.2	13.6	....	13.3	18.7	.....	93	.....	.....
2. Pulmonary stenosis and transposed pulmonary veins	IX	L. M., 11 M	4	...	138/2	13/7	125	14.3	16.5	15.6	15.3	P.V.* 19.4	19.4	P.V. 94	95	2:3
	X	G. I., 3½ M	3	...	50/8	30/18	20	12.9	13.0	12.8	12.2	Per.V.† 8.1	13.2	Per.V. 40	93	.....
3. Pulmonary stenosis and ventricular septal defect	XI	R. W., 18 M	0	...	35/2	12/4	23	16.0	16.1	17.3	17.4	.....	21.0	.....	87	2:3
	XII	S. M., 12 F	3	...	65/0	18/9	47	11.1	12.3	16.2	15.6	.....	18.0	.....	95	1:2
	XIII	D. K., 13 F	4	...	105/5	28/5	77	13.7	14.2	16.8	16.3	.....	Aorta 18.9	.....	Aorta 92	2:3
	XIV	P. G., 10 F	4	...	104/2	20/10	84	12.66	11.9	15.9	13.7	.....	16.6	.....	93	2:3

* P.V. = Pulmonary veins. LA = Left atrium. SVC = Superior vena cava.
† Per.V. = Peripheral vein. RV = Right ventricle. FA = Femoral artery.
RA = Right atrium. PA = Pulmonary artery.

CASE VI. R. L. A. was a thirty year old Caucasian male. He had had rheumatic fever at the age of four, at which time a cardiac murmur was detected. There had been no symptoms of heart disease but on admission to the hospital for another complaint the heart murmur was noted and a diagnosis of simple pulmonary stenosis was made.

Physical examination revealed a small, well developed man. The blood pressure was 100/65 mm. Hg. Arterial and venous pulses were of normal quality. The cardiac apex beat was in the normal site and of normal character. No abnormal pulsations were noted but a systolic thrill was evident in the second and third left intercostal spaces. The second heart sound at the pulmonary area was diminished. A grade IV systolic murmur was heard maximally in the second left intercostal space but radiated well into the left axilla and upwards towards the left clavicle.

An electrocardiogram showed a partial right bundle branch block pattern with evidence of right ventricular hypertrophy. First degree atrioventricular block was present.

The roentgenograms showed no general cardiac enlargement but the pulmonary artery segment and vascular markings were prominent.

Comment. Cardiac catheterization demonstrated a mild pulmonary stenosis; the left atrium was entered by the catheter and a left to right shunt and an increased pulmonary blood flow were demonstrated.

CASE VII. A. A. was a Caucasian male, age eleven years. A heart murmur was discovered at

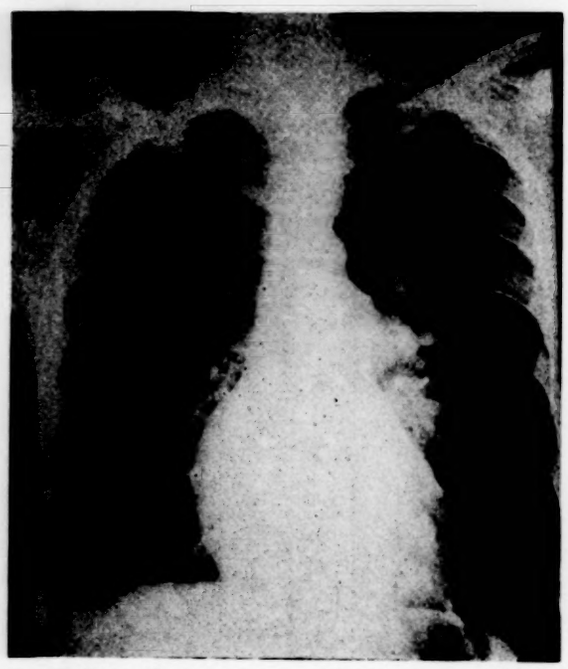


FIG. 1. Case I. Roentgenogram; pulmonary stenosis with atrial septal defect.

birth but there had been no symptoms of ill health.

Physical examination revealed a thin boy with a prominent left hemithorax. The pulse was normal and the neck veins showed no abnormal pulsations. The blood pressure was 105/65 mm. Hg. The apex beat was in the normal position and of normal character. A systolic thrill was palpable in the second and third left intercostal spaces. The second sound in the pulmonary area was diminished. A grade IV systolic murmur was heard maximally at the pulmonary area with radiation over the whole precordium and upper chest.

An electrocardiogram showed evidence of right ventricular hypertrophy.

The roentgenograms showed the absence of cardiac enlargement. The pulmonary artery segment was prominent and the films were considered compatible with a diagnosis of pulmonary stenosis.

Comment. Clinically, this appeared to be a case of simple pulmonary stenosis. Cardiac catheterization demonstrated the combination of pulmonary stenosis and atrial septal defect with a left to right shunt. The catheter was passed through the defect.

CASE IX. (Previously reported by Levinson and associates[16] (Case VII)). L. M. was a Caucasian boy, eleven years of age, with a history of recurrent sore throats, easy fatigue and slight shortness of breath on exertion.

Physical examination showed a poorly developed child with a prominence of the left chest. The arterial pulses were normal. Blood pressure was 105/65 mm. Hg. The venous pressure and pulsations were normal. The apex beat was in the normal position. A systolic thrill was felt over the second and third left intercostal spaces. The second heart sound was diminished in the pulmonary area and a harsh grade IV systolic murmur was heard in this region. The murmur was well transmitted into both axillas and up into the neck.

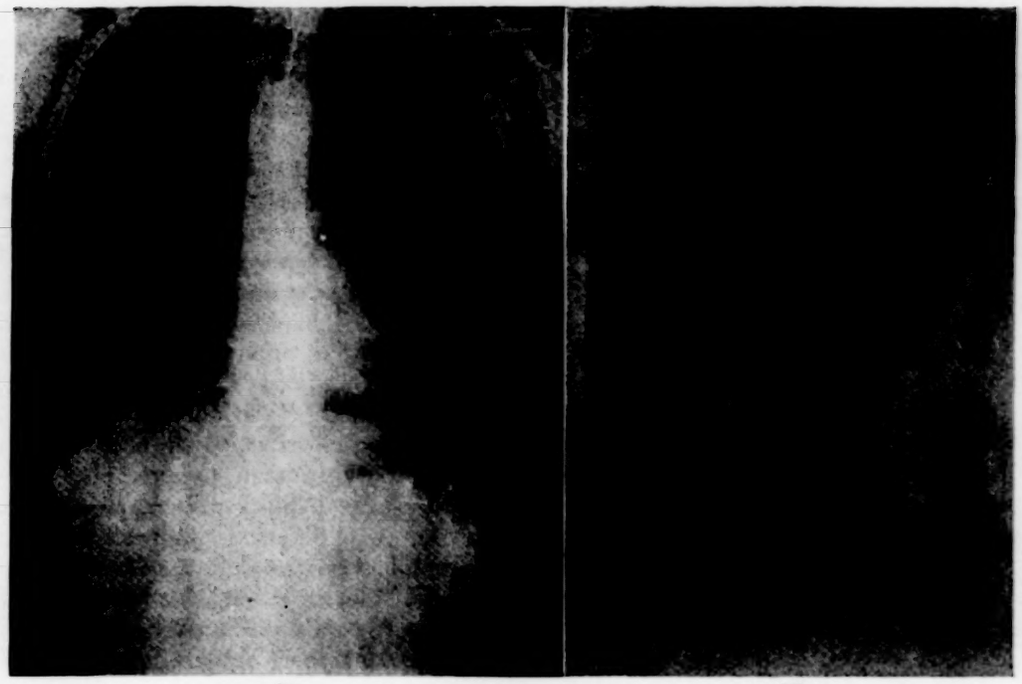
An electrocardiogram showed right ventricular hypertrophy.

The roentgenograms showed no cardiac enlargement but a slight dilation of the pulmonary artery segment was present. (Fig. 2.)

Comment. Cardiac catheterization revealed a moderately severe pulmonary valvular stenosis together with a significant rise in oxygen content in the right atrium. This case might have been considered an example of pulmonary stenosis with an interatrial shunt although the left atrium could not be entered. However, a transposed pulmonary vein communicating with the right atrium was penetrated and a diagnosis of pulmonary stenosis and transposed pulmonary vein was made. The degree of pulmonary stenosis was considered an indication for valvulotomy, which was successfully carried out by Dr. W. H. Muller.

CASE XII. S. M. was a Caucasian girl, age eleven years. When she was four years old the parents were told that a heart murmur was present. There had been no real restriction in her capabilities but she tired easily and became a little short-winded on exertion.

On physical examination she was a well nourished, healthy-looking girl. No abnormal venous pulsations were noted. The radial pulse was normal. The blood pressure was 100/70 mm. Hg. The apex beat was displaced just beyond the mid-clavicular line and a systolic lift was evident in the region of the third left intercostal space. A faint systolic thrill was present over the same space but no shock of pulmonary valve closure was felt. The heart sounds were normal. A grade IV systolic murmur was heard, loudest in the third and fourth intercostal spaces transmitted widely over the left chest. A faint, early diastolic murmur down the left sternal border was heard by some observers.



2A 2B

FIG. 2. Case VIII. A, roentgenogram; pulmonary stenosis with transposed pulmonary veins; B, catheter entering a right pulmonary vein from the right atrium.

The electrocardiogram showed right ventricular hypertrophy. The roentgenograms indicated generalized moderate cardiac enlargement. The pulmonary artery segment was dilated and at fluoroscopy the main branches of the pulmonary artery showed intrinsic pulsation.

Comment. A clinical diagnosis of ventricular septal defect was made. Cardiac catheterization confirmed the clinical diagnosis by revealing a significant rise in oxygen content in right ventricular and pulmonary arterial samples. In addition a pulmonary valvular stenosis was demonstrated. Peripheral arterial blood was 95 per cent saturated with oxygen.

CASE XIII. D. K. was a thirteen year old Caucasian girl known to have had a heart murmur since birth. With exertion or crying she had been noted to become cyanosed. Physical exertion was limited by easy fatigability and mild shortness of breath.

Examination revealed a plump girl in no distress. There was no evidence of cyanosis or clubbing of the extremities. No abnormal venous pulsations were seen. The pulse was normal. The blood pressure was 110/80 mm. Hg. There was no clinical cardiac enlargement. A systolic thrill was present in the second, third and fourth left intercostal spaces. The second sound in the pulmonary area could not be heard. A grade IV systolic murmur was heard over the area of the thrill.

An electrocardiogram showed right ventricular hypertrophy.

The roentgenogram was suggestive of some right ventricular enlargement while the pulmonary artery and its branches were within normal limits. (Fig. 3.)

Comment. Clinically, the findings were consistent with pulmonary stenosis although the low murmur and thrill suggested either an infundibular stenosis or a ventricular septal defect. Catheterization revealed a moderately severe valvular pulmonary stenosis. A significant rise in oxygen content in the right ventricle indicated a ventricular septal defect. This was further evidenced by passing the catheter through the defect into the aorta where the oxygen saturation was found to be 92 per cent. Angiocardiography indicated the probable presence of a valvular pulmonary stenosis but showed no right to left shunt or overriding aorta.

A successful pulmonary valvulotomy was performed by Dr. B. W. Meyer, who found no indications of a tetralogy at surgery.

RESULTS

The Clinical Syndrome. Severe cardiac symptoms were not experienced by any of these

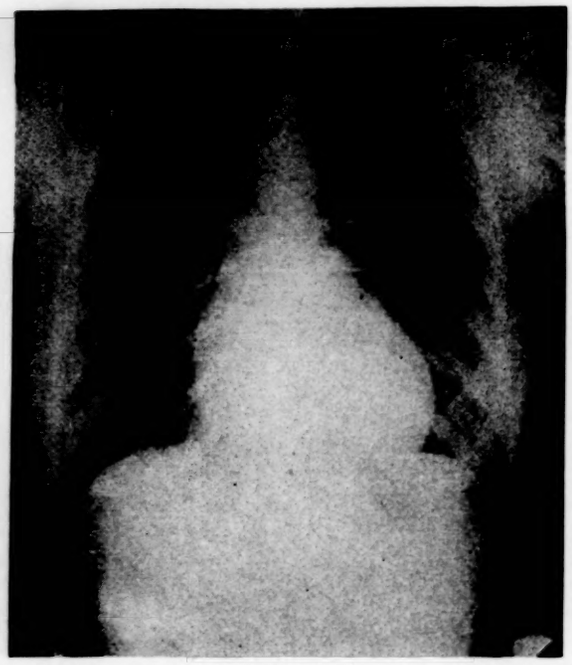


FIG. 3. Case XIII. Roentgenogram; pulmonary stenosis with ventricular septal defect.

patients. Seven were symptom-free while the remaining seven had mild breathlessness on exertion and a few patients complained of easy fatigability. An iatrogenic element or the influence of overanxious parents were evident factors in the genesis of symptoms in three cases. In only two cases, one P.S. + A.S.D. and one P.S. + V.S.D., was cyanosis on effort said to occur. In no patient could severe disability be said to exist.

On physical examination cyanosis and clubbing were absent in all cases. The arterial pulses were normal and in none was an elevated venous pressure seen. Giant "a" waves in the neck[14] and presystolic hepatic pulsation were never seen. Clinical cardiac enlargement was detected only twice in cases of P.S. + V.S.D. but a precordial heave suggestive of right ventricular hypertrophy was felt in four cases. Pulsation of the main pulmonary artery and the pulmonary valvular closing tap characteristic of pulmonary hypertension were absent. A basal systolic thrill was present in eleven cases and in all a systolic murmur of grade III intensity or greater was heard in the second or second and third left intercostal spaces. In three of the four cases of P.S. + V.S.D. the murmur and thrill were maximal in the third and fourth spaces. The second heart sound in the pulmonary area was quite variable in intensity; it was normal or diminished but in no case noticeably accentuated. The presence or absence of splitting of the second heart sound, considered a valuable sign in the diagnosis of moderate or severe pulmonary stenosis, was not routinely recorded but splitting was present in one case with a very mild degree of stenosis. Clinically, then, this group of cases presented the features of simple pulmonary stenosis of mild or moderate degree.

The electrocardiogram was normal in one of the cases of P.S. + V.S.D., a finding which has been reported previously in mild pulmonary stenosis[4,8] and in both P.S. + A.S.D. and P.S. + V.S.D.[4,11] In the remaining cases the twelve-lead electrocardiogram showed evidence of right ventricular hypertrophy or a right bundle branch block pattern or a combination of the two. Six cases showed the pattern of incomplete or complete (one case) right bundle branch block. While this pattern has been reported in mild pulmonary stenosis, pure right ventricular hypertrophy becomes more common as the severity of the stenosis increases.[4] The block pattern on the other hand is very frequent in atrial septal defects,[18] and was also found in four of five cases of P.S. + V.S.D. reported by Broadbent et al.[10] so that its presence may lend weight to the suspicion that pulmonary stenosis is complicated by a septal defect. Tall pointed P waves which are common in all types of severe pulmonary stenosis were not seen.

The radiologic studies confirmed the absence of cardiac enlargement in all but three cases. Enlargement of the pulmonary artery segment of slight to moderate degree was present in all except two children aged three and three and a half years, respectively. The routine radiologic reports suggested a significant increase in hilar vascular markings in five cases, and in two cases (one P.S. + A.S.D., one P.S. + V.S.D.) definite expansile pulsation of pulmonary artery branches was seen. The roentgenograms were finally independently reviewed by another radiologist without prior knowledge of the diagnosis. In four cases he considered the radiologic signs to be strongly in favor of an increased pulmonary blood flow.

In summary, the average clinical picture of the group was that of a relatively symptom-free individual with evidence of mild or moderate pulmonary stenosis. The signs of dynamically severe stenosis, cardiac enlargement, precordial heave, pure second sound, prominent "a" wave in the neck, hepatic pulsation and small volume

arterial pulses, were usually absent; the electrocardiogram frequently showed a right bundle branch block pattern slightly favoring the presence of a septal defect. Radiologically, dilation of the pulmonary artery segment was in keeping with a valvular pulmonary stenosis while the evidence of an increased pulmonary blood flow pointed to a left to right shunt. Clinical differentiation between the different types of shunt was not especially sought but a low murmur and thrill would appear to favor the presence of a ventricular septal defect.

CARDIAC CATHETERIZATION

1. Pulmonary Stenosis and Atrial Septal Defect. Pulmonary stenosis was demonstrated by a significant fall in systolic pressure on passing the catheter from the right ventricle into the pulmonary artery. Fluoroscopic examination of the site of pressure change and the appearance of the records suggested that the stenosis was valvular in all cases. The stenosis was always mild or moderate with a right ventricular systolic pressure well below 100 mm. Hg and a normal or even slightly elevated pulmonary artery pressure. If the degree of pulmonary stenosis is expressed in terms of the gradient between the right ventricular and pulmonary artery systolic pressure, the range in the group was 11 to 63 mm. Hg with an average of 32 mm. Hg, only two cases showing a gradient in excess of 50 mm. Hg. The right atrial pressure was normal in all cases averaging 2.5 mm. Hg. In five cases the left atrial mean pressure was measured; in one it equalled the right atrial pressure and in the others exceeded it by 1 or 2 mm. of mercury. In these cases the pressure gradient across the atrial defect necessary to maintain an over-all left to right shunt was present, a finding similar to that in uncomplicated atrial septal defect and the normal heart.[18,19]

2. Pulmonary Stenosis and Transposed Pulmonary Veins. Two cases were thought to fall within this group. Case IX has already been described and the hemodynamic findings are presented in Table II. This case was instructive in that the pulmonary stenosis was of severe degree with a right ventricular systolic pressure of 138 mm. Hg and a gradient of 128 mm. Hg between the right ventricle and the pulmonary artery. Despite the severe stenosis the right atrial pressure was not elevated and a gradient of 5 to 6 mm. Hg existed between the transposed pulmonary vein and the right atrium, thus permitting the pulmonary vein blood to enter the right atrium.

The second patient was a three and a half year old boy who underwent catheterization for suspected pulmonary stenosis. A mild stenosis was found and in addition, highly saturated blood was drawn from both chambers of the right heart, the pulmonary artery and superior vena cava; the peripheral venous sample showed a much lower oxygen content in keeping with venous blood. Although a transposed vein was not entered by the catheter, the findings are in keeping with previous experience of transposed veins.[16,20] The possibility that an occasional case labeled atrial septal defect is in fact an example of transposed pulmonary venous drainage into the right atrium or superior vena cava cannot easily be excluded if the left atrium has not been entered and, in any event, the combination of these two lesions is not rare. The problem of differentiation of these two conditions has been dealt with by Levinson et al.[16]

3. Pulmonary Stenosis and Ventricular Septal Defect. There were four examples of this association. Case XII showed a very mild stenosis with accompanying septal defect. The femoral arterial blood sample at the end of a long procedure showed an oxygen saturation of 87 per cent; the relatively low figure was interpreted as the result of the patient's shallow breathing and overenthusiastic use of sedatives. Cases XIII and XIV differ greatly from Cases XI and XII in that they showed a moderately severe stenosis with right ventricular systolic pressure of 105 and 104 mm. Hg and ventricular-pulmonary artery gradients of 77 and 84 mm. Hg, respectively. In Case XIII the systolic pressure measured with the catheter in the ascending aorta via the septal defect was 105 mm. Hg, and in Case XIV the routinely measured brachial artery systolic pressure was 105 mm. Hg. Thus in both cases the systemic and right ventricular systolic pressures were similar. Overriding of the aorta could not be demonstrated by angiocardiography in either case and the peripheral arterial oxygen saturation was 92 and 93 per cent, respectively. Case XIV differed from all the others in that the stenosis was considered to be infundibular as judged by the repeated demonstration of an intermediate pressure zone between the main right ventricle and the pulmonary artery. The angiocardiogram, however, demonstrated moderate poststenotic dilatation of the pulmonary artery, a finding which has been considered rare

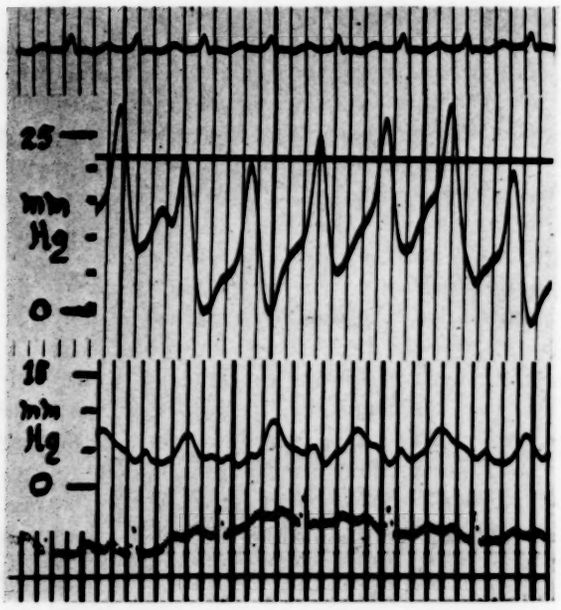


FIG. 4. Above, giant "a" waves from a case of severe simple pulmonary stenosis. Below, atrial pressure curve from a case of mild pulmonary stenosis and atrial septal defect.

in infundibular stenosis, so that the site of the stenosis was not definitely determined in this case.

DISCUSSION

The hemodynamic features of severe simple pulmonary stenosis and of pulmonary stenosis with reversed interatrial shunt have received much attention. In severe stenosis there is commonly a distinct rise in right atrial pressure, particularly during atrial systole with the result that a systolic wave measuring 15 mm. Hg may be seen (Fig. 4) in pressure tracings.[4,9,21,22] In this circumstance the giant "a" wave in the jugular pulse described by Wood[17] may be detected clinically as a vital physical sign. In cases with an atrial communication the high right atrial pressure serves either to open the flap-like foramen and permit a veno-arterial shunt or to alter the usual pressure gradient across a true atrial septal defect so that a reversed shunt occurs; in either event the right to left shunt is manifested clinically by cyanosis. It is evident that all cases of severe pulmonary stenosis with an interatrial shunt are potentially cyanotic; in some cases cyanosis exists from infancy while in others it is delayed, appearing in later years in consequence of the rising right atrial pressure.[23] In cyanotic cases in which the left atrial pressure has been measured, it has frequently been found to be below normal thus further accentuating the abnormal right to left pressure gradient.[4]

In the great majority of cases with a high right atrial pressure the stenosis is of severe degree with a right ventricular systolic pressure well in excess of 100 mm. Hg and with a low pulmonary artery pressure.[4,9] The pressure gradient between right ventricle and pulmonary artery in these cases is large. In five such cases seen in this laboratory the gradient averaged 105 mm. Hg with an average right atrial pressure of 18/5 mm. Hg. In nineteen cases with open foramen ovale described by Maraist et al.[9] the right atrial pressure averaged 17/5 mm. Hg and the right ventricular pressure 135/29. The right ventricular to pulmonary artery gradient averaged about 120 mm. Hg. In three severe cases without interatrial communication the right atrial pressure was 23/11, the right ventricular pressure 171/10 and the gradient about 160 mm. Hg.

A further feature of these cases with a high right atrial pressure is a slight to moderate rise in the right ventricular end diastolic pressure. This has been ascribed to the limitation of the normal distensibility of the right ventricle by progressive hypertrophy;[9,21,22] although the ventricle may empty adequately in systole, its limited distensibility may so alter the pressure-flow relationship between the atrium and ventricle that a rapid increase in pressure occurs during rapid inflow with exaggeration during atrial systole. Hypertrophy of the atrium and augmentation of its systolic contraction will be consequent upon an increase in atrial residual volume. Abrahams and Wood[4] have suggested that the forcible atrial contraction may aid in distending the right ventricle in late diastole and so enable it to raise the pressure necessary to overcome the resistance at the pulmonary valve; in this sense the elevated atrial systolic and ventricular end diastolic pressures may be looked upon as part of a physiologic overloading in keeping with Starling's law of the heart. Although viewed in this light, the mechanism may aid ventricular discharge, cases with these findings may show a diminished cardiac output[4,9] and the occasional occurrence of effort syncope and rapidly progressive right heart failure indicates that hypodynamic action of the ventricle may readily occur.

Selzer and Carnes[24] have recently reviewed the role of pulmonary stenosis in the production of chronic cyanosis. They pointed out that in all autopsied cases showing pulmonary stenosis and

interatrial communication with chronic cyanosis the defect consisted of a typical foramen ovale. In the majority the valvular foramen would only have permitted a right to left shunt, and for this reason they preferred the term pulmonary stenosis with patent foramen ovale to pulmonary stenosis with reversed interatrial shunt.

This series of cases is presented, and contrasted with the type of pulmonary stenosis which is severe and may be accompanied by a right to left shunt, in order to suggest consideration of the group as a distinct clinical entity. It is suggested that the future course of such lesions may not involve progression of the pulmonary stenosis, and thus that they behave and will continue to behave as a benign lesion. With this in mind surgical treatment for the stenosis has not been recommended. Certainly, in the presence of a left to right shunt the mild pulmonary stenosis may protect the patient from increasing pulmonary hypertension. The finding of a very slightly elevated pulmonary artery pressure in some of the present cases has been noted previously in uncomplicated pulmonary stenosis by Silber et al.[25] who considered it evidence of elevated vascular resistance, possibly the result of maldevelopment of the pulmonary vascular tree.

TABLE III

COMPARATIVE FEATURES OF FOUR TYPES OF PULMONARY STENOSIS WITH NORMAL AORTIC ROOT

	Simple Pulmonary Stenosis—Mild	Simple Pulmonary Stenosis—Severe	Pulmonary Stenosis with Reversed Interatrial Shunt	Pulmonary Stenosis with Atrial Septal Defect
Symptoms				
Dyspnea	0	+ (or 0)	+ (or 0)	0 (or +)
Fatigability	0	+	+	0
Cyanosis on effort	0	0	Present at rest	?
Syncope	0	Occasionally	Occasionally	0
Physical signs				
Cyanosis, clubbing, polycythemia	0	0	+ to +++	0
Giant "a" wave	0	+	+	0
Cardiac enlargement	0	0 to +	0 to +	0
Right ventricular heave	0	+	+	0
Second sound	Usually normal	Single	Single	Usually normal
Murmur and thrill	+	+	+	+
Electrocardiogram	Normal RBBB pattern Slight RV hypertrophy No "P" pulmonale	RV hypertrophy (severe) "P" pulmonale RBBB pattern	RV hypertrophy (severe) "P" pulmonale RBBB pattern	RV hypertrophy RBBB pattern (normal)
Radiologic findings				
Enlargement	0	0 or + to +++	0 or + to +++	0 or +
Pulmonary artery	+	+	+	+
Vascularity	Normal	Diminished	Diminished	Normal or increased
Hilar pulsation	0	0	0	May be present
Cardiac catheterization				
RV systolic pressure	Below 100 mm. Hg	Above 100 mm. Hg	Above 100 mm. Hg	Below 100 mm. Hg
RV-PA systolic gradient	Less than 90 mm./L.	More than 90 mm. Hg	More than 90 mm. Hg	Less than 90 mm. Hg
Right atrial pressure	Normal	May be elevated	May be elevated	Normal
Left atrial pressure	Normal	Diminished ?	Diminished	Normal
Ratio systemic/pulmonary blood flow	1:1	1:1	More than 1:1	Less than 1:1

In strong contrast to these findings and mechanisms in severe pulmonary stenosis, the cases with interatrial communication in the present group showed the clinical and hemodynamic features of a much milder degree of pulmonary stenosis. All right atrial and right ventricular diastolic pressures were normal. Thus an over-all left to right shunt was permissible, and in the light of the work of Selzer and Carnes, a true atrial septal defect is suggested. Cyanosis was never present; and, in fact, one of the distinguishing features of the group presented is the scarcity of clinical symptoms. Enlargement of the heart was rarely present, and the systolic murmur in the pulmonary area was the only constant clinical finding. In almost all cases the diagnosis of a mixed lesion, i.e., the presence of the combination of atrial septal defect and pulmonary stenosis could not be made with certainty until cardiac catheterization was performed. (Table III.)

The two cases of transposed pulmonary veins in combination with pulmonary stenosis are reported primarily to complete this group. A single transposed vein rarely constitutes a hemodynamic problem, placing little additional burden on the right ventricle. A significant hemodynamic and therapeutic problem is

present only when transposed pulmonary veins are multiple, in which case they often are accompanied by an interatrial septal defect. In the cases cited herein the surgical indications were determined wholly on the basis of the degree of pulmonary stenosis.

The four cases of ventricular septal defect and pulmonary stenosis represent an unusual group. In two the right ventricular pressure and systemic pressure were similar, resembling the five cases described by Broadbent et al.[11] The finding of mean right ventricular pressures between 30 and 40 mm. Hg in five of Abrahams' and Wood's[4] young patients suggests that a similar situation might have been found if the systemic pressures had been measured. The association of pulmonary stenosis with normal aortic root and ventricular septal defect with balanced right- and left-sided pressures may be more common than hitherto suspected. These cases may be regarded as potentially cyanotic, as judged by the occurrence of cyanosis on effort in Case XIII and in several of the others which have been described.[4,11]

The surgical implications of pulmonary stenosis with ventricular septal defect are important. It may be argued that relief of stenosis in these cases may lead to a great increase in the left to right shunt and a failure to gain the expected improvement; Case XIII in this series, with balanced right and left ventricular pressures, derived definite subjective improvement from pulmonary valvulotomy but has not been recatheterized. Valvulotomy has also been advised in Case XIV, the severity of the stenosis being taken as the indication for the operations in the absence of precise knowledge of the subsequent course of these patients.

SUMMARY

1. A series of cases exhibiting the combination of pulmonary stenosis and a defect permitting a left to right shunt is described. The series includes examples of the combination of pulmonary stenosis with atrial septal defect, transposed pulmonary veins and ventricular septal defect, respectively.

2. The clinical features of the cases were in general those of mild or moderate pulmonary stenosis. It is thought that electrocardiographic and radiologic findings may suggest the presence of an accompanying septal defect.

3. Atrial septal defect with left to right shunt occurred in the presence of mild or moderate pulmonary stenosis and a normal left to right atrial pressure gradient. These findings are contrasted with those in pulmonary stenosis with right to left shunts.

4. A shunt through transposed pulmonary veins may occur in the presence of severe pulmonary stenosis.

5. Cases of ventricular septal defect and pulmonary stenosis appeared to fall into two groups; those with slight to moderate elevation of right ventricular pressure and those in which the right ventricular and systemic pressures were similar.

6. The surgical implications of these combined lesions are discussed.

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Some Variations in the Clinical Picture of Congenital Defect of the Interventricular Septum

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THE most commonly described picture of congenital ventricular septal defect is that characterized by little or no cardiac enlargement, a systolic murmur, often with a thrill, of maximal intensity in the third and fourth left intercostal spaces adjacent to the sternum and a normal electrocardiogram.[1-3] Although it is admitted that large defects may be characterized by right ventricular enlargement, increase in size of the pulmonary arteries, cyanosis and clubbing,[2] little is mentioned by most authorities of other variations in the clinical picture.

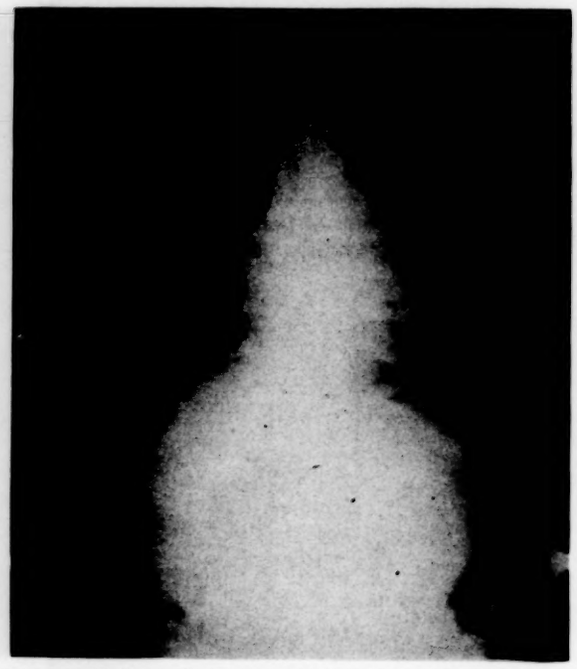


FIG. 1. Patient L. B., age three and one-half years; ventricular septal defect. Postero-anterior teleroentgenogram shows some cardiac enlargement and normal pulmonary vascular pattern.

It is the purpose of this paper to describe seven patients with ventricular septal defect, all studied by cardiac venous catheterization, who present some of the numerous variations in clinical findings possible in this condition. In addition an eighth patient is described whose entity clinically resembled ventricular septal defect but who was found to have other unsuspected anomalies by cardiac catheterization.

The variations described here are familiar to workers in the field of congenital heart disease[4,5] but it is believed that the general internist is sufficiently unaware of them to warrant their presentation.

The patients described are from the medical and pediatric services of the Brooklyn Hospital. Case IV is from the pediatric service of the Kings County Hospital. Case VII is from the cardiac laboratory of the Cincinnati General Hospital.

Cardiac venous catheterizations were done in the conventional manner.[6] Pressures were recorded by means of Sanborn electromanometers and Poly-Viso electrocardiograph. Blood samples were analyzed in the Van Slyke apparatus and duplicates were required to check within 0.2 cc./100 cc. Expired air samples were collected in Douglas bags and analyzed in the Scholander micro gas analyzer.

CASE REPORTS

CASE I. L. B., a three and one-half year old boy, was seen September 17, 1953. A systolic cardiac murmur was discovered at birth. No cyanosis had been seen. The patient had some coughing and dyspnea on exertion. Appetite and weight gain were fair.

At physical examination the blood pressure was 70/40 and the weight 32 pounds. The patient was slender but normally developed. No cyanosis or clubbing was seen. A harsh systolic murmur and thrill were found; these were most intense in the fourth left intercostal space

adjacent to the sternum and at the cardiac apex. The aortic second sound was louder than the pulmonic second sound. Femoral pulses were strong.

Electrocardiogram showed no axis deviation. No evidence of right or left ventricular hypertrophy was seen and all complexes were normal. Cardiac x-ray revealed a slight right and left ventricular enlargement and a normal pulmonary vascular pattern. (Fig. 1.)

The results of the hemodynamic studies are seen in Table I. One right atrial sample showed a rise in O_2 content over the superior caval sample. There was a significant rise in O_2 content in right ventricular over right atrial blood. The slight further rise in the pulmonary arterial blood oxygen content was insignificant. There was no pulmonary hypertension. Systemic arterial oxygen saturation was within normal limits. Eisenmenger's syndrome could be excluded by the normal right ventricular pressure. The findings were consistent with isolated ventricular septal defect.

Comment. The location of the murmur, cardiac configuration and normal electrocardiogram fit well into the classic picture of ventricular septal defect. The faint pulmonary second sound was the only unusual feature.

CASE II. M. V., a seventeen year old Puerto Rican boy, was seen September 21, 1953. He was referred because of a cardiac murmur discovered a few weeks previously during a routine preemployment physical examination. There was no history of heart disease or rheumatic fever. Slight exertional dyspnea had been noted for three months; otherwise, he was asymptomatic.

At physical examination blood pressure was 110/60. The patient was normally developed. There was no cyanosis or clubbing. The heart was not definitely enlarged. There was a grade 5 systolic murmur, with a thrill, maximal in the third and fourth left intercostal spaces adjacent to the sternum. The aortic second sound was louder than the pulmonic second sound. Femoral pulses were strong.

Electrocardiogram was normal and no axis deviation was observed. Cardiac x-ray showed no evidence of cardiac enlargement. Questionable hilar pulsations were seen. There was a normal pulmonary vascular pattern. (Fig. 2.)

Results of hemodynamic studies are seen in Table I. There was a rise of 1.1 volumes per cent in O_2 content of the right ventricular blood sample as compared with the right atrial sample

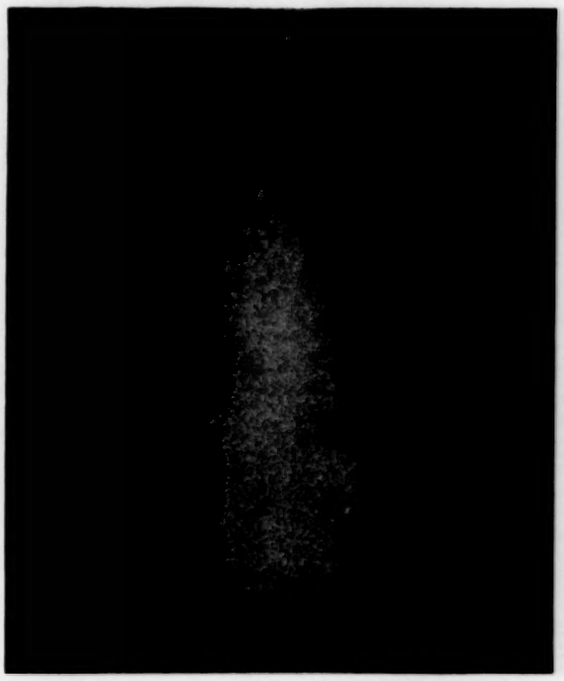


FIG. 2. Patient M. V., age seventeen years; ventricular septal defect. Postero-anterior teleroentgenogram shows no cardiac enlargement, but some straightening of left upper cardiac border in pulmonary artery region; normal pulmonary vascular pattern.

nearest the tricuspid valve. This, together with the clinical picture, was consistent with left to right shunt through a ventricular septal defect. Without the clinical picture this finding would be less significant. The systemic arterial oxygen saturation was normal. There was no pulmonary hypertension or stenosis. Pulmonary flow was 8.1 L./min. Effective pulmonary flow was 5.9 L./min. Left to right shunt was 2.2 L./min.

Comment. This patient also fits into the classic conception of the clinical picture of ventricular septal defect. The location of the murmur and thrill, the normal cardiac silhouette on x-ray and the normal electrocardiogram are all part of the picture.

CASE III. J. S., a two and one-half year old boy, was seen October 19, 1953. During his first year of life he had frequent respiratory infections. At the age of one year, he had pneumonia and was discovered to have a cardiac murmur. No cyanosis was noted. Exercise tolerance was fair.

At physical examination the blood pressure was 106/61 and weight 28 pounds. No cyanosis or clubbing was found. There was a fairly marked pigeon breast. The heart was enlarged to the left. A precordial systolic murmur was noted, loudest

FIG. 3. Patient J. S, age two and one-half years; ventricular septal defect. Postero-anterior teleroentgenogram shows marked cardiac enlargement, pulmonary vascular engorgement and dilatation of main pulmonary artery.

in the third and fourth intercostal spaces adjacent to the sternum. An apical diastolic gallop was heard. The pulmonary second sound was louder than the aortic second sound. Femoral pulses were normal. The liver was enlarged three and one-half fingerbreadths below the right costal margin. The tip of the spleen was palpable.

Electrocardiogram revealed an incomplete right bundle branch block; a notched R wave in lead V_1 with an intrinsicoid deflection of 0.06 seconds. No Q or S wave was present in lead V_1. There was also first degree A-V block, the P-R interval of 0.15 seconds being prolonged for the heart rate and age. Left axis deviation was present. Cardiac x-ray showed an increase in pulmonary vascular markings with intrinsic hilar pulsations. There was marked enlargement of the left ventricle and lesser enlargement of the right ventricle. (Fig. 3.)

Hemodynamic studies are listed in Table I. There was a marked rise in blood oxygen content in passing from right atrium to right ventricle. Marked pulmonary hypertension was noted, but overriding aorta could be fairly well excluded by the lower systolic pressure in the right ventricle than in a peripheral artery. The systemic arterial oxygen saturation was slightly below normal. The findings are indicative of a large left to right shunt through a ventricular septal defect with probable shunt from right to left as well.

Comment. Although the location of the murmur and the left as well as right ventricular enlargement suggested ventricular septal defect in the patient, the electrocardiographic findings and the history of frequent respiratory infection are often seen in atrial septal defect. The location of the murmur, the absence of increased pulse pressure and the catheterization findings seemed to exclude patent ductus arteriosus, although occasionally an aortogram is necessary to make the distinction. Enlargement of both ventricles may be seen in large ventricular septal defects but is unusual in a small ventricular septal defect.

CASE IV. R. S., a three and one-half year old girl, was seen June 29, 1953. A cardiac murmur was discovered at the age of five months; when she was seven months old, her parents were told that she had congenital heart disease. She was cyanotic only during temper tantrums. Growth and development had been normal.

At physical examination blood pressure was 100/55 and weight 31 pounds. There was normal development without cyanosis or clubbing. A systolic murmur and thrill were found over the precordium, most intense in the fourth and fifth left intercostal spaces adjacent to the sternum. The aortic second sound was louder than the pulmonic on some occasions; on others, the pulmonic was louder. Femoral pulses were strong.

Electrocardiogram revealed no axis deviation. The complexes were all normal except for lead V_1 in which the QRS showed a notched R wave with a delayed downstroke suggesting incomplete right bundle branch block. Cardiac x-ray showed increased pulmonary vascularity but definite hilar pulsations were not seen. Both ventricles were enlarged, the left more so than the right. (Fig. 4.)

Hemodynamic studies are listed in Table I. There was a considerable increase in blood oxygen content in the right ventricle over the right atrium. Although some further rise in the pulmonary artery was noted, it was believed that this was due to poor mixing rather than to a patent ductus arteriosus. There was moderate pulmonary hypertension. Systemic arterial oxygen saturation was normal. The findings are consistent with an isolated ventricular septal defect with shunt from left to right only.

Comment. Here the location of the murmur and the balanced electrocardiogram are consistent with the classic clinical picture of ventric-

ular septal defect. However, the marked cardiac enlargement, especially of the left ventricle, and increase in lung vascularity, although described in this condition, are not part of the classic picture. The hemodynamic data alone could conceivably be found with patent ductus arteriosus but the location of the murmur is strong evidence against this possibility.

TABLE I

HEMODYNAMIC DATA IN VENTRICULAR SEPTAL DEFECT

Case No.	Patient	Age (yr.)	O_2 Content cc./100 cc. Blood*							Arterial Saturation	Arterial Pressures (mm. Hg)				
			SVC	IVC	RA	RV	PA	FA BA	Aorta		RA Mean	RV	PA Mean	PA Sys/Dia.	BA
I	L. B.	3	12.1	10.3	11.9 13.0	14.6 15.0	15.3 15.3	15.6	....	93%	3.0	31/7	17	28/9	70/40†
II	M. V.	17	13.3	....	13.3 13.5 13.9	14.4 13.7	14.4 14.7	17.6	....	99%	0.7	20/1	8	13/4	110/60†
III	J. S.	2½	8.7	7.3	8.7 9.7	12.9 13.1	12.9 13.4	13.5	....	90%	5.0	75/6	62	85/43	106/61
IV	R. S.	3	10.0	10.5	10.1 10.3	12.6 13.2	13.1 14.0	15.8	....	99%	4.5	42/?	29	39/19	123/72
V	M. N.	14	12.6	13.4	13.3 14.7	17.9	17.0 15.6	17.8	....	94%	7.8	35/7	17	27/8	101/63
VI	W. M.	7	11.7	10.6	11.7 12.0	15.0 14.1	14.8 14.5 14.7	15.5	....	94%	3.4	38/8	26	36/18	95/50†
VII	C. M.	19	9.9	....	8.5	11.8	11.7	....	....	94%	7.8	‡	17.5	.....	120/75†
VIII	G. E.	6	12.2	....	12.1 12.7	15.6 17.9 17.2 17.8	17.8	18.5	17.8	92% (Rest) 89% (After exercise)	2.1	84/3	8.5	13/5	84/57§

* SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; PA, pulmonary artery; FA, femoral artery; BA, brachial artery.

† Cuff pressure.

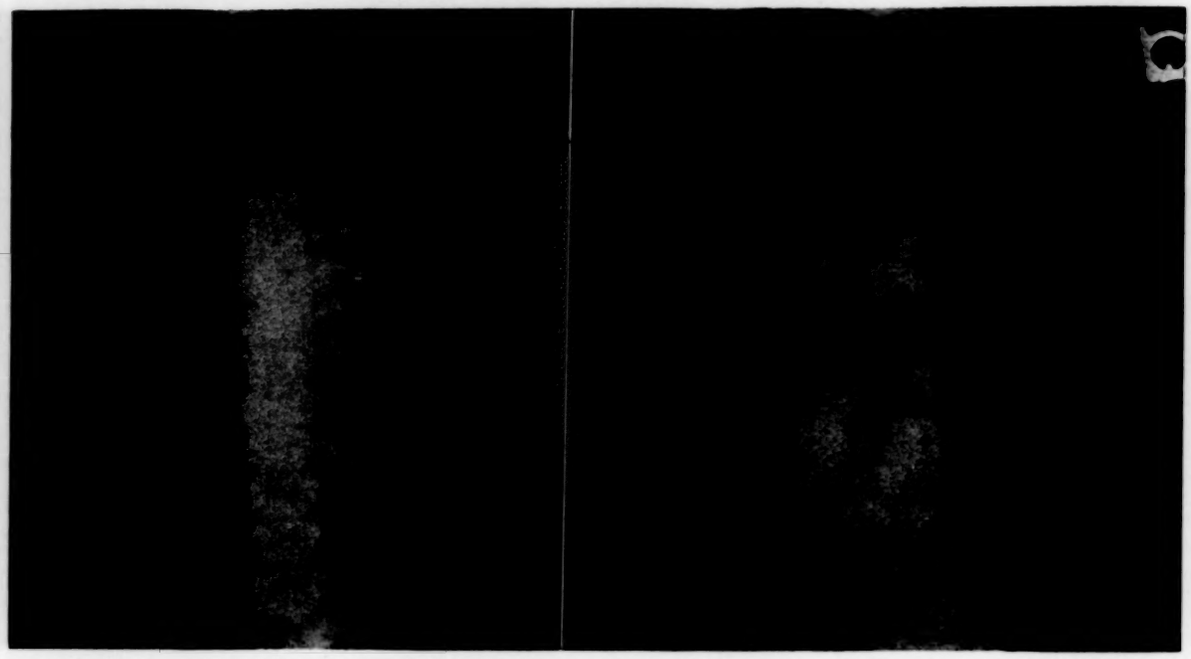
‡ No significant difference in systolic pressures in right ventricle and in pulmonary artery.

§ Aortic pressure.

CASE V. M. N., a fifteen year old girl, was seen September 9, 1952. A cardiac murmur was discovered at the age of three when she had pneumonia. There had been no other hospitalizations. She had never been cyanotic or dyspneic. Growth and development were normal.

At physical examination blood pressure was 115/80. The patient was normally developed without cyanosis or clubbing. The heart did not seem enlarged. A grade 4 systolic murmur was present with a thrill maximal in the second and third left intercostal spaces. The pulmonary second sound was accentuated and split. There was a transient apical mid-diastolic murmur. Femoral blood pressure was 140/90.

Electrocardiogram revealed the following: The QRS complex was of normal duration. The right precordial leads showed an rSR′ pattern with an intrinsicoid deflection of 0.06 seconds and indicated either incomplete right bundle branch block or right ventricular hypertrophy. Left axis deviation was present. Spatial vectorcardiogram showed counterclockwise inscription of the QRS loop in the horizontal plane and indicated right bundle branch block. Cardiac x-ray showed enlargement of the outflow tract of



4A 4B

FIG. 4. Patient R. S., age three and one-half years; ventricular septal defect. A, postero-anterior teleroentgenogram showing marked cardiac enlargement with increased pulmonary vascular markings; B, left anterior oblique view showing marked left ventricular enlargement.

the right ventricle and pulmonary artery. The pulmonary vasculature was prominent; intrinsic hilar pulsations were present. (Fig. 5.) No enlargement of the left cardiac chambers was present.

Hemodynamic studies are presented in Table I. The blood oxygen contents showed a slight step-up in the right atrium over the superior and inferior caval average. This was considered to be of possible significance. There was a marked step-up in blood oxygen content in the right ventricle. Arterial oxygen saturation was normal. There was no pulmonary hypertension. The findings are indicative of a large left-to-right shunt through a ventricular septal defect. It is possible that there is as well a small atrial septal defect or anomalous pulmonary vein draining into the right atrium. Pulmonary flow was 21.7 L./min. Effective pulmonary flow was 6.7 L./min. Left to right shunt was 15 L./min.

Comment. Clinically, this patient resembled closely the classic pattern of atrial rather than ventricular septal defect. The location of the murmur, the loud split P_2, the intrinsic hilar pulsations, right ventricular enlargement, and the electrocardiogram suggestive of incomplete right bundle branch block are all common in atrial septal defect. However, catheterization studies left little doubt that ventricular septal defect was the chief anomaly. It is of further interest that right ventricular enlargement occurred without pulmonary hypertension. Apparently the increased pulmonary flow and right ventricular work caused by the shunt are responsible.

CASE VI. W. M., a seven year old boy, a Mongolian idiot, was seen October 15, 1952. A cardiac murmur was discovered at the age of six months. He had pneumonia at the age of sixteen months. No cyanosis or dyspnea were ever noted. The boy had not developed mentally in a normal manner; his power of speech was limited to a few monosyllables.

At physical examination blood pressure was 95/50. The patient had the stigmata of Mongolian idiocy. There was a grade 5 systolic murmur together with a thrill of maximal intensity in the third and fourth left intercostal spaces adjacent to the sternum. P_2 was not prominent but was louder than A_2. No cyanosis or clubbing was found.

On electrocardiogram lead V_1 showed an RSR′ pattern with a QRS of 0.08 second, and was consistent with incomplete right bundle branch block. Cardiac x-ray revealed accentuation of pulmonary vascular markings with right ventricular hypertrophy.

Hemodynamic studies are listed in Table I.

The blood oxygen contents showed a marked step-up in going from the right atrium to the right ventricle. There was moderate pulmonary hypertension. Arterial oxygen saturation was normal. The findings are consistent with an isolated ventricular septal defect with left to right shunt.

Comment. The location of the murmur and thrill were typical of ventricular septal defect. However, the electrocardiographic findings of incomplete right bundle branch block and the roentgen demonstration of enlargement of the right ventricle and pulmonary vascular overload are not usually described.

CASE VII. C. M., a nineteen year old boy, was seen December 11, 1951. This case was previously reported.[7] A cardiac murmur was discovered during a routine physical examination made prior to removal of a bone cyst. There was no history of cardiac disability; there was some mental retardation.

On physical examination blood pressure was 120/75. No cyanosis or clubbing was present. The general examination was negative except for the heart. There was a grade 3+ systolic murmur heard over the entire precordium, maximal in the second left intercostal space next to the sternum. A third heart sound or short apical mid-diastolic murmur was heard. P_2 was not accentuated.

Electrocardiogram was normal and no axis deviation was present. Cardiac x-ray revealed a prominent pulmonary artery. There was no cardiac chamber enlargement.

Hemodynamic studies are presented in Table I. There was a marked step-up of blood oxygen content in going from right atrium to right ventricle. There was no pulmonary hypertension. Systemic arterial oxygen saturation was normal. Left-to-right shunt was 2.9 L./min.; total pulmonary flow was 5.5 L./min. The findings are indicative of left-to-right shunt into the right ventricle through a ventricular septal defect.

Comment. The cardiac silhouette and electrocardiogram were, in this case, consistent with the usual picture of ventricular septal defect. However, the high location of the cardiac murmur is unusual, the murmur usually being maximal in the fourth left intercostal space adjacent to the sternum, rather than in the pulmonary area. The hemodynamic data leave little doubt that an isolated ventricular septal defect is the lesion responsible for the murmur.

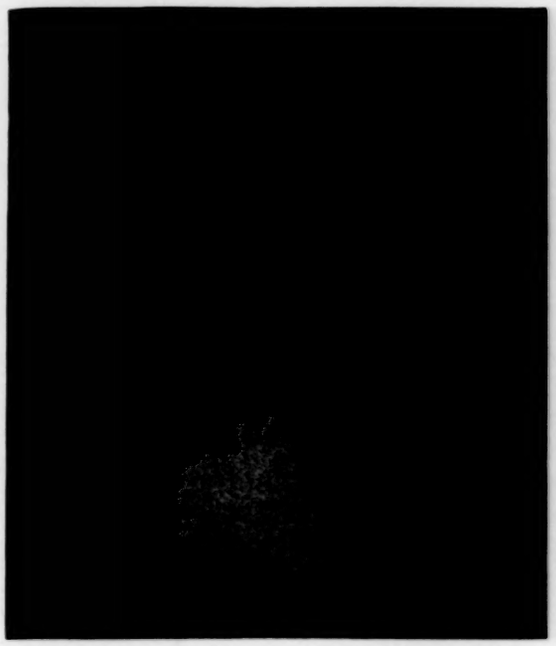


FIG. 5. Patient M. N, age fifteen years; ventricular septal defect. Postero-anterior teleroentgenogram shows some cardiac enlargement with dilatation of main pulmonary artery and increase in pulmonary vascular markings.

CASE VIII. This case differs from the foregoing in that the patient appeared clinically to have an isolated ventricular septal defect but on catheterization studies was found to have the components of the tetralogy of Fallot.

The patient, G. E., a five year old boy, was seen October 1, 1952. A cardiac murmur was found shortly after birth. The only bout of cyanosis was associated with a respiratory infection in 1951. There had been frequent attacks of pneumonia, pharyngitis and tonsillitis. Appetite was poor and physical development retarded.

At physical examination blood pressure was 88/50 and weight 34 pounds. This patient was small for his age. There was no cyanosis or clubbing. The heart showed a grade 4 systolic murmur and a thrill maximal in the second left intercostal space adjacent to the sternum. The pulmonic second sound was louder than the aortic but was fainter than normal. Femoral pulses were normal.

Electrocardiogram showed right axis deviation and right ventricular hypertrophy. Spatial vectorcardiogram was consistent with right ventricular hypertrophy. Cardiac x-ray (Fig. 6) revealed an enlarged right ventricle. The anteroposterior film was not well centered. Pulmonary

FIG. 6 Patient G. E., age five years; tetralogy of Fallot. Postero-anterior teleroentgenogram shows slight concavity in main pulmonary artery region with no reduction in pulmonary vascular markings.

vascular markings were prominent but no hilar dance was seen.

Hemodynamic studies are listed in Table 1. There was a marked increase in blood oxygen content in going from right atrium to right ventricle. Arterial oxygen saturation was only slightly below normal and showed very little drop with exercise. The catheter was advanced into the aorta from the right ventricle. The low pulmonary arterial pressure and high ventricular systolic pressure indicated pulmonary stenosis. The data indicated pulmonary stenosis, overriding aorta and ventricular septal defect, and thus the tetralogy of Fallot.

Comment. On clinical examination this boy appeared to have an isolated septal defect, either atrial or ventricular. The high location of the murmur favored atrial septal defect. The finding of pulmonary stenosis came as a surprise because of the prominent pulmonary vascular markings; the finding of overriding of the aorta was unexpected because of the virtually normal arterial oxygen saturation with little change on exercise. The arterial oxygen saturation of 92 per cent at rest and 89 per cent on exercise presented by this boy are quite unusual in the tetralogy of Fallot. Bing, Vandam and Gray[8] studied thirty-eight cases of tetralogy of Fallot. Of these only one had an arterial oxygen saturation above 90 per cent; in this instance the resting arterial oxygen saturation was 91 per cent, but there was a fall to 74.5 per cent with exercise. The failure of arterial oxygen saturation to fall significantly with exercise suggests that the overriding is not important functionally in this boy insofar as right to left shunting of blood is concerned.

DISCUSSION

In consideration of the rapid advances in cardiac surgery, including recent reports of operative correction of the condition under discussion, it is apparent that accurate diagnosis of ventricular septal defect, as well as of other forms of congenital heart disease, is of paramount importance.

In attempting to make a diagnosis of isolated defect of the interventricular septum by cardiac catheterization one must be careful to exclude additional overriding of the aorta (Eisenmenger's syndrome) and patent ductus arteriosus. In the cases presented, the difference in systolic right ventricular and brachial arterial pressures sufficed to eliminate the possibility of overriding aorta. In addition all save one had a normal systemic arterial oxygen saturation. Damman and Sell[9] have shown that hemodynamic studies in patent ductus arteriosus may mimic ventricular septal defect where there is much pulmonary valvular insufficiency; likewise a high ventricular septal defect may mimic patent ductus arteriosus on catheterization study. This is not common, however, and occurred only twice in their series of seventeen cases, which were of a type in which this difficulty is most likely to occur. In our group the low site of the systolic murmur and the absence of a diastolic murmur served to exclude patent ductus arteriosus when there was doubt concerning the hemodynamic studies. Occasionally an aortogram is necessary to establish the presence or absence of patent ductus arteriosus.

In two instances, the question of an additional atrial septal defect or anomalous pulmonary venous drainage was raised because of some increase in oxygen content of right atrial blood samples over those from the vena cava. Although such a possibility cannot be eliminated by the data available, we have arbitrarily used the criterion of Burwell and Dexter[9] in these patients, i.e., to be significant, a right atrial sample must show an increase in oxygen content over

1.9 volumes per cent above that in the superior vena cava. By this criterion the changes were significant in one patient. There was definite evidence of a larger ventricular shunt in this patient. There was no evidence of tricuspid insufficiency in the right atrial pressure tracing of either patient.

In several patients in the present series, the pulmonic second sound was at times faint enough to raise the question of additional pulmonary stenosis. This possibility was eliminated in these instances by cardiac catheterization, which showed no significant gradient between systolic pressures in the right ventricle and pulmonary artery. The mechanism of this diminution in the pulmonic second sound is obscure. It has been postulated that in some instances the systolic murmur extends into early diastole and may thus obscure partially the second sound.

In three instances a short mid-diastolic noise was heard at the cardiac apex. In two instances this was interpreted as a murmur; in the other as a gallop. It has recently been stated that the increased flow through the left side of the heart in left to right shunts of this type may produce a diastolic murmur at the cardiac apex which is due to relative mitral stenosis.[4]

It is of interest that there was in one instance rather marked right ventricular hypertrophy without pulmonary hypertension. It has been pointed out that atrial and ventricular septal defects may be associated with right ventricular hypertrophy as a result of increased pulmonary flow in the absence of pulmonary hypertension.

It must be stated that the patients discussed here are a selected series; it is highly unlikely that there is as much variation in the whole population of ventricular septal defects as is seen here. However, it is believed that these variations are not uncommon. It is likely that the patients having considerable cardiac enlargement had larger defects than the average.

SUMMARY

In seven patients the diagnosis of ventricular septal defect as an isolated lesion was established by the clinical picture and by cardiac catheterization. An additional patient resembled ventricular septal defect clinically but was found on catheterization study to have the tetralogy of Fallot.

In the seven instances of isolated ventricular septal defect, the following clinical picture was found:

1. There was in each patient a systolic cardiac murmur. This was of maximal intensity in the second, third or fourth intercostal spaces adjacent to the sternum. A thrill was felt in systole in five of seven patients. No diastolic murmur was heard at the left sternal border, but a short apical diastolic murmur or gallop was heard in three patients.
2. The pulmonic second sound varied from diminution to accentuation with splitting.
3. The pulmonary vascular markings varied from normal to accentuation with intrinsic pulsation. Intrinsic pulmonary hilar pulsations were seen fluoroscopically in two instances and were questionable in a third.
4. The cardiac silhouette on x-ray was virtually normal in two; showed right ventricular hypertrophy in two; in three showed combined hypertrophy of both ventricles, chiefly the left.
5. The electrocardiogram was normal in three instances and showed incomplete right bundle branch block in four instances.
6. Cyanosis and clubbing were absent in all patients. All save one had a normal arterial oxygen saturation.

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Myocardial Ischemia during Mitral Commissurotomy*

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Cardiac arrhythmias have been reported by many authors during thoracic surgery[1–12] and cardiac catheterization.[13–15] These arrhythmias may originate from anesthesia, vagal stimulation, anoxemia and hypoxia, as well as from direct manipulation of major cardiovascular structures during thoracic surgery. The arrhythmias that develop during mitral commissurotomy may arise from a combination of many of these factors, with the possible addition of direct interference to blood flow through the left coronary artery.

We are reporting in detail five instances in which such interference with the coronary flow seemed important in the initiation of serious cardiac arrhythmia during operations on the mitral valve. One additional patient showed a similar picture but the electrocardiographic tracing was unfortunately lost. These six patients were selected from a group of thirty cases studied electrocardiographically during performance of mitral valvulotomy. In the remaining twenty-four patients no serious arrhythmias were detected.

Observations were made by means of a direct single channel writing Sanborn electrocardiograph and a monitoring oscilloscope.† Significant areas of the tracing were recorded by means of the direct writing instrument when this seemed indicated.

The patients were all thought to be suffering from mitral stenosis, in some instances combined with mitral insufficiency. Their ages varied from twenty-four to fifty-eight. Each had been fully evaluated by cardiac catheterization according to the technic described elsewhere.[23]

Anesthesia consisted of induction by sodium pentothal or nitrous oxide-oxygen-ether with maintenance on an ether-oxygen mixture. This anesthesia seems satisfactory for cardiac surgery since high oxygen levels can be obtained and the vagal activity is depressed. Periodically the lungs are completely inflated especially if there are any signs of increased cardiac irritability which is not obviously related to manipulation of the heart. This reinflation is designed to minimize respiratory acidosis consequent to inadequate pulmonary ventilation. In a few cases procaine was injected into the pericardial sac prior to its incision but this has recently been dispensed with because its prophylactic value is questionable and at times it seemed to initiate arrhythmias. The use of cardiotonic drugs such as atropine, pronestyl, prostigmine and epinephrine was minimized.

The electrocardiographic abnormalities which we are discussing in these patients resemble those seen in anterior coronary occlusion. It must be noted at the outset, however, that only one lead was taken in these cases. Because of technical difficulties and the transitory nature of the abnormalities, it was impossible to obtain simultaneous leads from other extremities. Ideally, a multigraph type of recording system would be employed.

There are a number of other influences which confused the electrocardiographic picture. Sixty-cycle line interference occurred often with manipulation of the mediastinum, especially when many instruments were introduced into the chest and came into contact with the heart. The suction apparatus was a conspicuous offender stimulating auricular or ventricular premature beats, and artefacts simulating static build-up.

The pattern seen in anterior coronary occlusion is well known.[16,17,27] The R wave in lead 1 becomes low and an abnormal Q wave appears.

† Constructed by Missouri Electronics Corporation, St. Louis, Mo.

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The S-T segment becomes elevated and the T wave becomes diphasic or inverted. In lead 3 reciprocal changes may occur, with depression of the S-T segment and inversion. Lead AVL shows a QR pattern with S-T segment changes; AVR and AVF may also have RS-T segment changes. These changes will vary with heart position and will depend upon whether the leads are facing the surface of the infarct and/or the ischemic area. Precordial leads will show abnormal Q waves and elevated RS-T segments.

It is commonly believed[16,27] that the "dead zone" or infarcted area is responsible for the Q deflection or the QRS changes encountered in myocardial infarction. Therefore, without QRS changes a definite electrocardiographic diagnosis of infarction should not be made. Burch and Winsor have stated: "A shift of the S-T segment is due to a current of injury or is due to the zone of injury and the zone of ischemia is responsible for the T wave changes observed in infarction." General opinion indicates that the QS-QR wave signifies myocardial death.

In both experimental and clinical coronary occlusion, the first electrocardiographic evidence is an evaluation of the S-T segment in the appropriate leads. This is usually followed by T wave inversion and appearance of a Q wave; the latter is thought to represent death of muscle through the entire thickness of the myocardium.

Prinzmetal[25] has reported findings somewhat at variance with the conventionally accepted opinion, moreover observations by others[19,20] have indicated that the QS or QR pattern does not always follow the expected path. Baker[27] seems to imply that subendocardial myocardial infarction may cause an initial deflection of QRS, but also a late R wave of less than normal amplitude is inscribed. In Prinzmetal's reports[18,25] the QS wave on several occasions was found to be present over regions containing viable muscle. Also, the QR waves failed to appear in those experiments in which chronic endocardial infarcts and acute lesions did not involve the epicardial surface.

We are aware of only two reports of transient injury pattern in the electrocardiogram during intrathoracic surgery.[9,24]

The pertinent operative and electrocardiographic findings in five of the six patients are summarized in the following reports. In the sixth patient the electrocardiographic tracing resembled that of the others but, unfortunately, the record was discarded. Other patients may have shown transient changes which were not recognized early in the series. For the sake of brevity, the clinical evidence for mitral stenosis has been omitted from the histories. Figure 1 illustrates the position of the clamp on the left auricular appendage and the relationship of the back portion of the jaws of this clamp to the left coronary artery. It is readily seen that any pressure of this clamp against the heart can interfere with the flow of blood through the left coronary artery.

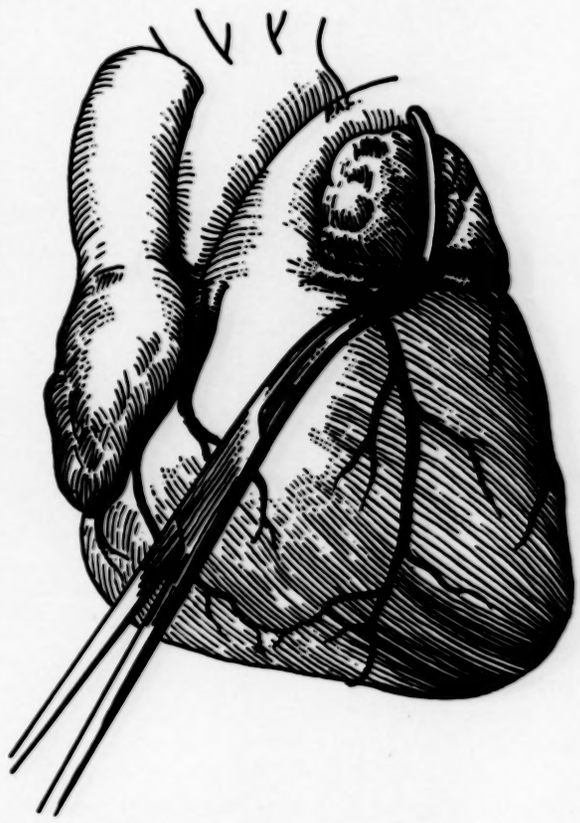

FIG. 1. Occluding clamp in place on the left auricle showing relation of the back of the clamp to the left coronary artery.

CASE REPORTS

CASE 1. A twenty-seven year old girl with electrocardiographic evidence of right ventricular hypertrophy had a pressure in the pulmonary artery of 116/58 mm. Hg at rest and 178/62 mm. Hg with exercise. Operation was performed on June 9, 1952. The electrocardiographic tracings taken throughout the procedure were limited to lead 1.

Figure 2A is a reproduction of a tracing taken just before opening the thoracic cavity. This

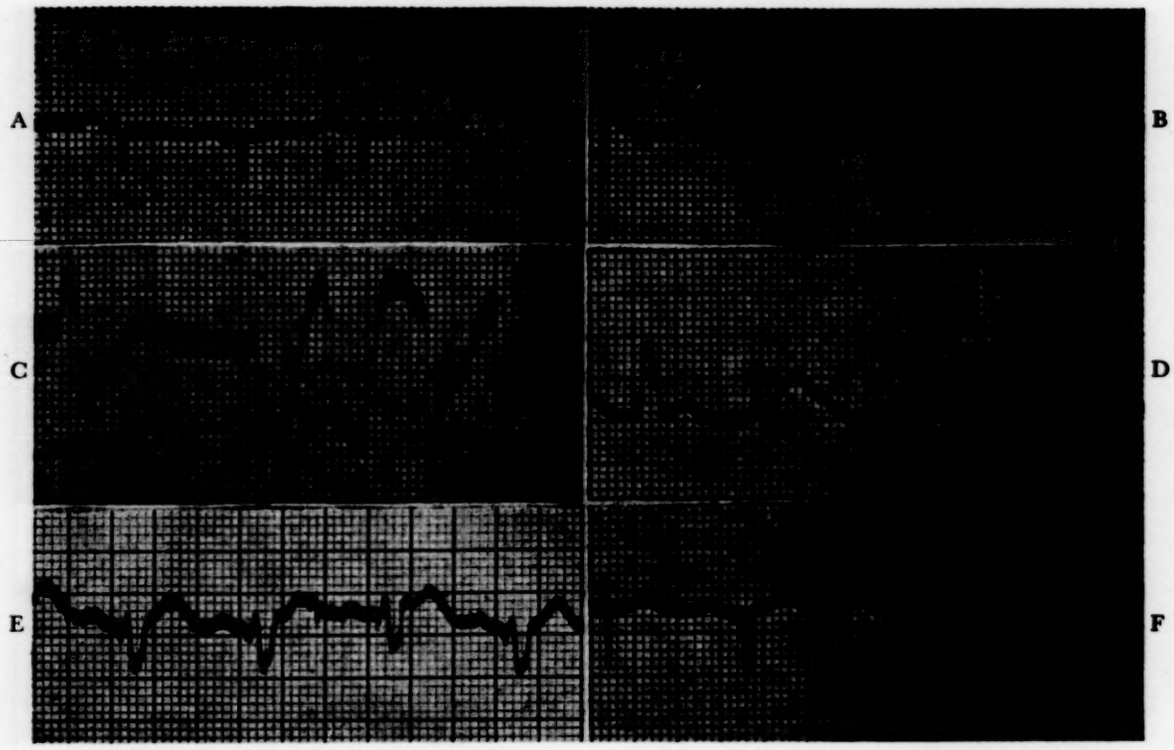

FIG. 2. Lead I taken in all tracings. A, prior to opening of thoracic cavity; B, after occluding clamp applied and first changes of "coronary" pattern; C, intermittent ventricular tachycardia and fibrillation; D and E, immediately after cessation of ventricular fibrillation; F, at time of closure of the thoracic cavity.

pattern remained unchanged until the occluding clamp was placed on the left auricular appendage. Significant ST-T changes occurred at this time but were not noted immediately since this was early in our series when we were more intent on the ventricular arrhythmias. Soon the changes became more obvious, as is indicated in Figure 2B. Here one can see the well formed QR with the ST-T changes usually seen with anterior myocardial infarction. This pattern changed in a moment to runs of ventricular tachycardia and ventricular fibrillation. (Fig. 2C.) This quickly cleared when the position of the clamp was shifted and the following tracing (Fig. 2D) shows the changes after the pattern of ventricular tachycardia and fibrillation had ceased. During closure of the auricular appendage a right bundle branch block developed temporarily (Fig. 2E) but in the final tracing during closure of the thoracic cavity (Fig. 2F) the electrocardiogram returned essentially to normal. Subsequent electrocardiograms during the postoperative period did not reveal any abnormalities.

Comment. This is an example of ventricular tachycardia and fibrillation which regressed spontaneously without specific therapy when the causative agent was removed. In this case the initiating stimulus was pressure on the left coronary artery by the back of the occluding auricular clamp.

CASE II. A thirty-two year old woman with evidence of right ventricular hypertrophy and pressures in the pulmonary artery of 96/39 mm. Hg at rest and 116/44 mm. Hg with exercise was operated upon in September, 1952. All tracings in these figures are with the AVL lead. Figure 3A shows a normal tracing which was taken prior to any manipulation of the heart although the thoracic cavity had been opened. In the second tracing (Fig. 3B) one sees the sudden development of a definite QR pattern with change in the ST-T segment. This occurred when the occluding clamp was placed on the auricle. When the surgeon shifted the clamp after being informed that the electrocardiogram showed abnormalities the condition improved. However, at the end of operation complete revision to the normal pattern had not yet occurred. (Fig. 3C.) After one week (Fig. 3D) there was still questionable change, but in seven weeks no residual remained. (Fig. 3E.)

Comment. This is an example of myocardial injury and ischemia at the end of operation but clearing eventually. The acute, short ST-T deflection was quickly corrected by a shift in position of the clamp on the left auricular appendage.

CASE III. This forty-one year old woman with right axis deviation by electrocardiogram and with pressures in the pulmonary artery of 40/17 mm. Hg at rest and 68/21 mm. Hg with exercise underwent commissurotomy on October 14, 1952. Figure 4A shows the AVR lead (taken throughout) prior to any direct manipulation of the heart. However, during clamping of the auricular appendage changes in the QR-ST-T segment developed as seen in Figures 4B and C. These changes subsided slowly after ischemia had been relieved by removal of the clamp. (Fig. 4D.) After completion of the valvulotomy, Figure 4E shows a questionably normal tracing. On the following day (Fig. 4F) there was no evidence of changes due to ischemia, nor were any noted in subsequent weeks.

Comment. In this case ischemic changes persisted slightly longer than usual after removal of the clamp but no residual was seen on the following day or in subsequent weeks.

CASE IV. This forty-two year old man had a left axis deviation with a pressure of 30/18 mm. Hg in the pulmonary artery at rest and 54/29 mm. Hg with exercise. Valvulotomy for mitral stenosis was performed on November 2, 1952. Despite the left axis deviation, the diagnosis of "pure" mitral stenosis was confirmed at operation. The tracing in Figure 5A (all tracings being AVL) was taken during incision of the chest wall and shows no abnormalities. Because of excessive sixty-cycle line interference only two complexes are shown to illustrate ST-T wave changes (Fig. 5B) which began to subside immediately after relief of pressure on the left coronary artery. (Fig. 5C.) Figure 5D was taken two weeks later.

Comment. This is a good example of the extremely transient nature of these ischemic complexes when the initiating cause is removed by alerting the operating surgeon. In some instances there remains a slight elevation of the ST-T segment and T inversion at the end of operation; these changes clear completely.

CASE V. This thirty-nine year old woman had pressures of 31/22 mm. Hg in the pulmonary artery at rest and 52/32 mm. Hg with exercise. Commissurotomy was performed on March 7, 1953. Using the AVL lead a tracing taken before the skin incision shows the small RS and upright T pattern. (Fig. 6A.) After the clamp had been placed on the auricular appendage the second tracing (Fig. 6B) demonstrates early QR and ST-T segment changes which rapidly progress through the next three stages ending in ventricular fibrillation. (Figs. 5C to E.) After the customary measures of intermittent cardiac compression and defibrillation[8,21,22,26] the sixth tracing

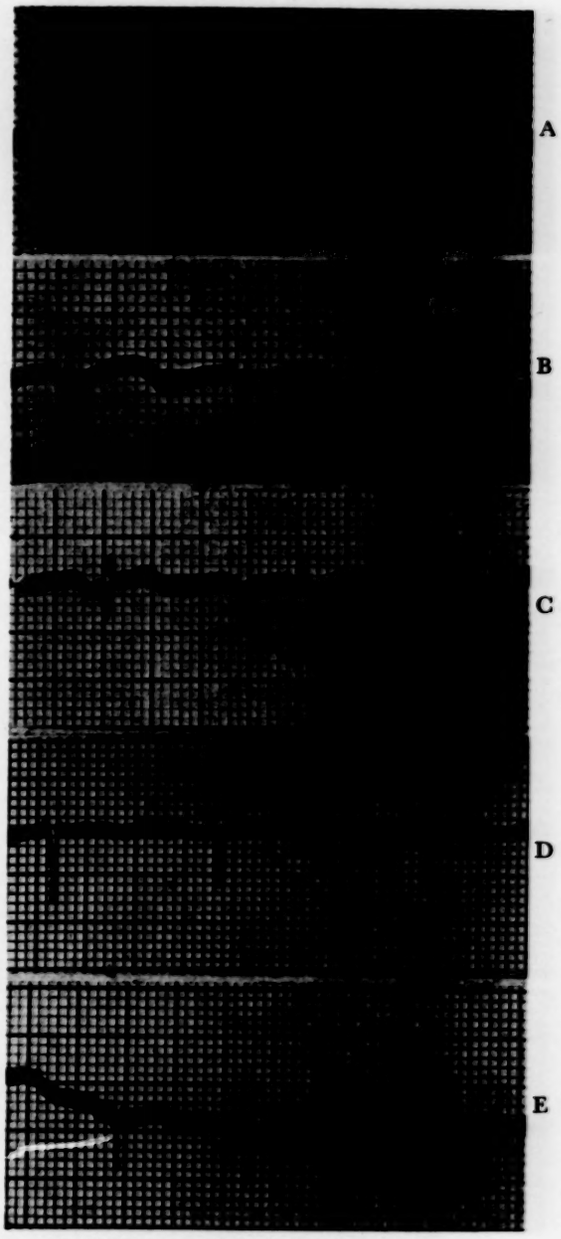

FIG. 3. (AVL throughout.) A, prior to any contact with the heart; B, with clamp on left auricular appendage; C, immediately after operation; D, one week after operation; E, seven weeks after operation.

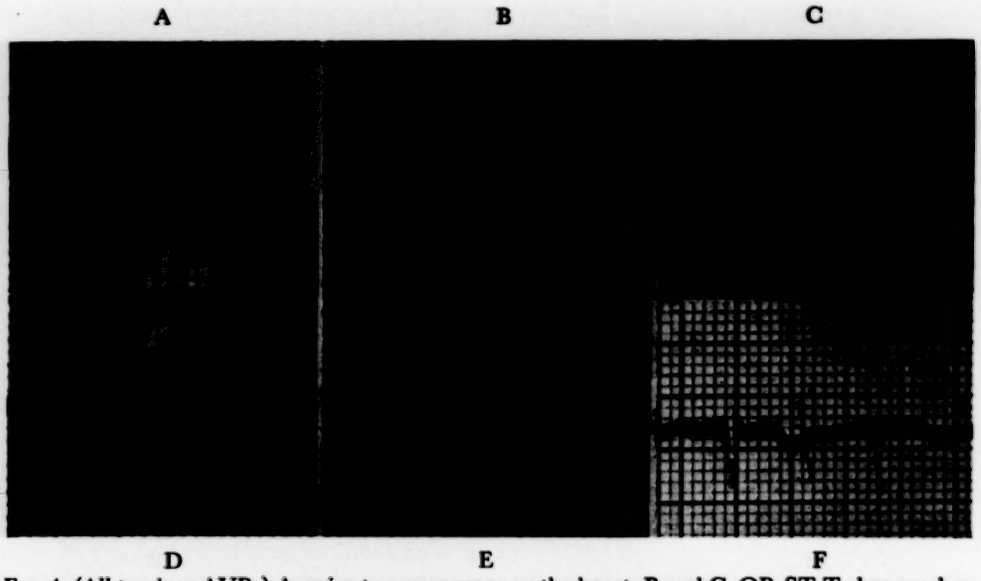

FIG. 4. (All tracings AVR.) A, prior to any surgery on the heart; B and C, QR-ST-T changes during manipulation with clamp on auricular appendage; D, shortly after clamp pressure on auricle removed; E, during closure of thoracic wall; F, following day.

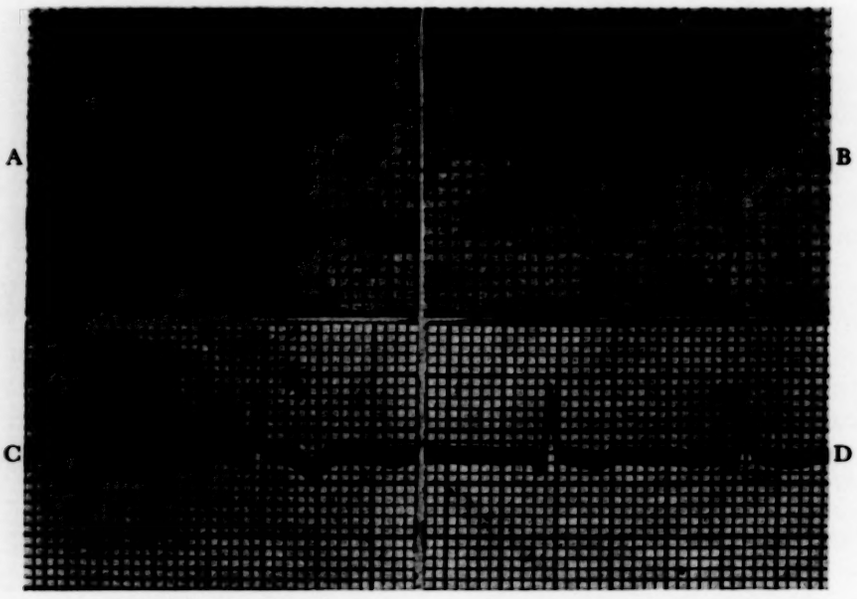

FIG. 5. (Each tracing AVL.) A, prior to surgery; B, during manipulation of the heart with clamp in position on the left auricular appendage; C, a few moments later; D, two weeks after operation.

(Fig. 6F) reveals deep Q and ST-T changes. After the surgery had been completed a small R wave reappeared preceding the S wave but the ST-T segment was still involved. (Fig. 6G.) The two other tracings (Fig. 5H and I) were taken on successive days postoperatively; they show no residual evidence of myocardial infarction although some ischemia remains as manifested by ST-T depression and inversion.

Comment. This was a severe myocardial ischemia which led to ventricular fibrillation requiring cardiac "massage" and electrical defibrillation. Certain abnormalities were still visible in the two days after operation.

DISCUSSION

In all of these patients the tracings which have been reproduced demonstrate changes similar

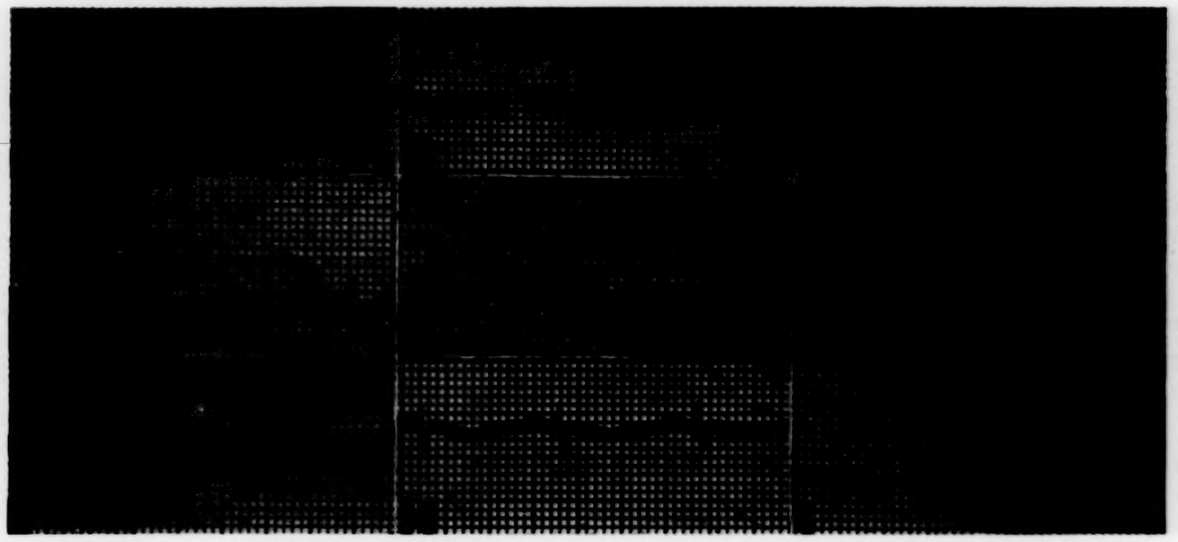

FIG. 6. (All tracings are AVL.) A, prior to any surgery on the heart; B, early changes of "coronary" pattern; C, later changes; D, just prior to ventricular fibrillation; E, ventricular fibrillation; F, immediately after defibrillation; G, upon closure of thoracic cavity; H, first day after surgery; I, second day after surgery.

to those seen in anterior myocardial infarction. However, no postoperative complications simulating coronary insufficiency have resulted. In all instances these changes occurred during manipulation of the left auricle, particularly when the occluding clamp was applied to the auricular appendage. It is not definitely established whether these changes are due to direct pressure on the left coronary artery or to traction on the surrounding structures of such degree that the artery is secondarily constricted. In many cases it would appear to be direct pressure on the left coronary artery by the rotation of the clamp toward the right side of the patient in the hands of the first assistant. The intimate association of the left coronary artery, particularly its circumflex branch, to the base of the auricular appendage is well known. Attempts during operation to reproduce this pattern by direct pressure in the region of the anterior descending branch of the coronary artery have been suggestive but such attempts have naturally been limited by the obvious danger associated with such testing.

The exact mechanism in the various cases has not been elucidated. In certain instances, however, particularly when the auricle has been torn during operative manipulations and it has been necessary to apply the clamp deeply to the auricle, it is apparent that the likelihood of compromising the coronary circulation is increased. It cannot be overemphasized that the lack of multiple electrocardiographic leads hinders determination of the exact mechanism present in these cases. While it is not possible to state positively that this is a "coronary occlusion" pattern, we believe there is fairly reliable indication of myocardial ischemia. The most likely cause of this ischemia is interference with circulation through the left coronary artery because of the auricular clamp.

The occurrence of a Q wave for only brief periods is contrary to the generally accepted theory that the Q wave indicates death of the myocardium. We have no clear explanation of this phenomenon but the transitory nature of the Q wave seen in these tracings may be explained by the extreme sensitivity of the oxygen deficiency so that it becomes physiologically "dead" and incapable of conducting impulses. Still being viable, the myocardium returns to a normal physiologic state with prompt restoration of oxygen supply. It is possible that direct interference with coronary circulation by this mechanism is a more common cause of arrhythmia than has previously been recognized. Careful electrocardiographic monitoring of the heart during the phase of auricular clamping and manipulation may permit detection of these changes before they have gone on to serious or possibly fatal ventricular arrhythmias.

SUMMARY AND CONCLUSIONS

From an electrocardiographic study of thirty patients undergoing surgery for mitral stenosis, we have presented the records of five patients

who showed electrocardiographic evidence of myocardial ischemia during clamping of the left auricular appendage. This phenomenon was noted in an additional case which is not reported in detail.

It seems pertinent to stress the value of these electrocardiographic changes as a premonitory sign of impending ventricular fibrillation during mitral commissurotomy.

This confirms the advisability of careful electrocardiographic observation during certain phases of the operative attack on the mitral valve.

Acknowledgment: We wish to express our gratitude to Dr. D. B. Flavan for his assistance and criticism in the preparation of this paper.

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The Histogenesis of Arteriosclerosis of the Larger Cerebral Arteries, with an Analysis of the Importance of Mechanical Factors*

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As we have previously pointed out,[10] those concepts of the genesis of arteriosclerosis which have the widest acceptance at the present time fall short of providing an adequate explanation of the mode of development of this disease in man. In large part this is due to lack of appreciation of factors of susceptibility, the great variability in microscopic structure of human arteries and human arteriosclerosis, and the physical forces which play an important role in the pathogenesis of the disease. Several investigations indicate that even so fundamental a problem as whether lipids initiate the formation of intimal plaques or are only a by-product of the development of the latter has not been solved.[7,12,14]

The experimental production of atheromas cannot be expected to furnish information regarding the nature of human arteriosclerosis unless the following criteria are eventually met: (1) The distribution of lesions is similar to that observed in man; (2) the sequence of formation of the various elements in the plaque is similar to that in the human disease; (3) the microscopic characteristics of plaque and wall are also similar; (4) the experimental procedure reproduces a situation known to obtain in the human; and (5) complications such as thrombosis, aneurysm formation or rupture of arteries result when severe lesions are produced.

Despite the abundance of literature on the subject of arteriosclerosis, it appears that even the initial phase, namely, complete understanding of the pathologic characteristics of the human disease, has not been attained. It has therefore been the purpose of our studies to attempt to provide additional information regarding the pathology and possible pathogenesis of human arteriosclerosis in order to establish adequate criteria for proper evaluation of experimental work. In these studies we have considered the total wall, not just the intimal layer. The present report is a continuation of a comparative study of the pathologic characteristics of human arteriosclerosis in various parts of the arterial circulation. Previous reports have demonstrated striking differences in the histologic pattern of development of arteriosclerosis in these various sites and in their susceptibility; these studies have dealt with the aorta, pulmonary, coronary, renal, splenic and hepatic arteries, and with the arterial tree of the lower extremity.[2–4,10,13,15,18]

From these observations and the application of certain established physiologic principles, the concept has been developed that arteriosclerosis represents an adaptive response, structural as well as biochemical, to physical forces which act over long periods of time. The use of the term "aging" in previous reports has not been intended in a strict chronologic sense but only to denote the time factor which must be coupled with the acting physical forces. Because such forces are in a sense traumatic, we have also used the term "wear and tear" to express the cause of certain histologic responses which have been observed. The latter involve not only the intima but also the whole arterial wall.

The present report deals specifically with the major arteries which make up the circle of

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Willis of the cerebral circulation. Several considerations motivated this study: (1) Ease of accessibility of these arteries makes possible their removal without injury and with minimum distortion; (2) this segment of the arterial circulation can be compared with those previously studied; (3) certain inherent structural weaknesses exist which may be expected to intensify the arteriosclerotic process if the latter is conditioned by physical forces; (4) racial comparisons can be made as in preceding reports.[2,10,13]

TABLE I
AGE AND RACE DISTRIBUTION OF CASES FOR MICROSCOPIC STUDY

Age Group (yr.)	White	Negro
0–19	7	0
20–39	33	3
40–59	15	14
60–79	37	5
80 and over	10	0
Total	102	22

MATERIAL AND METHOD

This study was divided into two parts. The first consisted of a study of the microscopic aging pattern of the basilar artery. Longitudinal and cross sections obtained from 124 basilar arteries (age and race distribution shown in Table I) were examined. Comparisons were made in each instance of adjacent sections, one stained with hematoxylin and eosin, a second by the Weigert-Verhoeff technic for elastic tissue and the third prepared by microincineration. The details of method have been previously described.[4] Because no significant sex differences were found, no breakdown according to sex has been given. When a sufficient number of cases permitted, a comparison was made of the intensity of pathologic changes in Negro and white groups of corresponding ages as in previous reports.

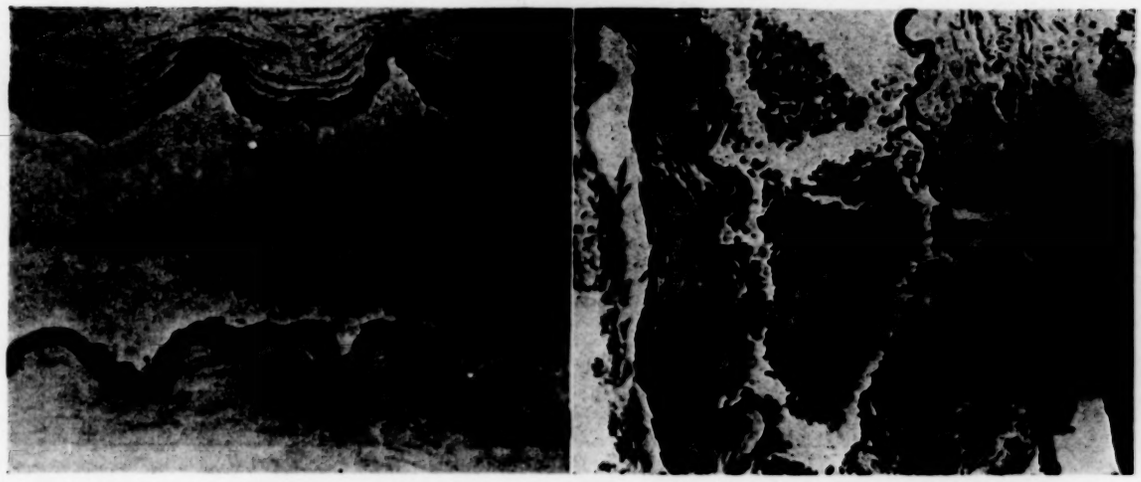
The second portion of this study consisted of a careful gross examination of thirty-seven circles of Willis from white individuals only. Locations of plaques were carefully mapped and internal and external diameters of arteries measured. The latter was accomplished by means of a dissecting microscope equipped with a calibrated ocular. In general, three to four sites through various portions of the length of an artery were taken; these were trimmed to segments about 0.25 cm. in thickness and placed on the platform of the microscope for measurement. An average of measurements from such segments was taken as the average internal and external diameter of the artery. In addition, marked variations from the average in distribution and size were recorded.

The arteries thus measured were divided into two age groups as shown in Table II. The measurement of the average internal radius was used in calculating the hydrostatic tension according to the Laplace equation as applied by Burton.[5] The details of the application of this formula have been previously reported.[18] In these calculations the mean pressure within arteries of the circle of Willis was taken to be 80 mm. Hg (1.3×10^{-3} dynes). The tensions thus calculated were correlated with the relative dilation and increase in thickness with advancing age, as shown in Table II, as well as with the frequency of plaque formation. In this way we have been able to obtain an expression of the gross effects of physical forces upon arteries.

RESULTS

Microscopic Aging Changes in the Basilar Artery

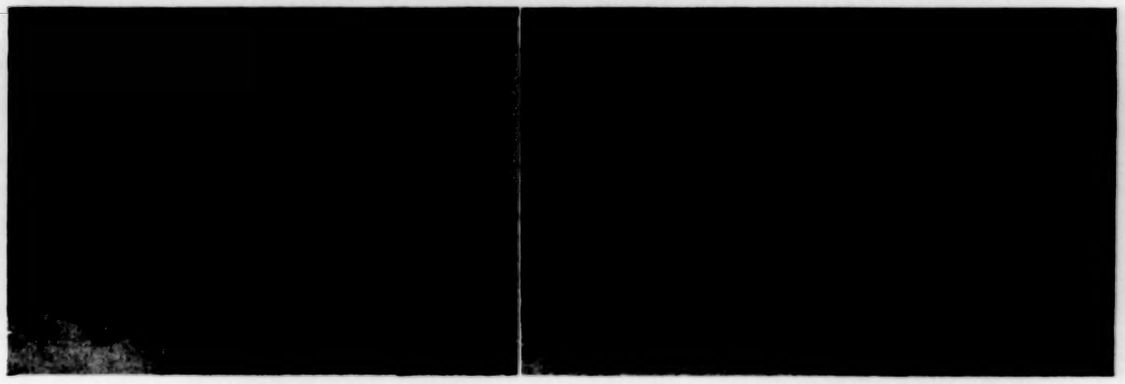
Age Group 0–19 Years (Seven Cases). As in other arteries, the internal elastic lamella of the basilar arteries of newborn infants was located immediately beneath the endothelium and rested directly on the medial muscle. The internal elastic lamella was thicker than in arteries previously studied and showed a peculiar beaded appearance not observed in previous studies. (Fig. 1.) Such beading was found in five of the seven cases in this age group. During the second decade of life the intimal layer in some cases occupied as much as 5 per cent of the thickness of the wall, but several showed wide areas without intima. There were occasional areas of reduplication of the internal elastica; this was most marked near the mouths of branches, where fibroelastic cushions were occasionally formed. Such cushions were seen even in a newborn infant. (Fig. 2.) The media was devoid of elastic elements except in two cases in which a few fine filaments were found. In none of the cases did the adventitia contain an organized external elastic lamella; in only one instance a few fine elastic filaments were observed in this area.



1 2

FIG. 1. Basilar artery of five year old female. Magnification approximately × 480. Note periodic beading of internal elastica and beginning formation of an elastic filament at A.

FIG. 2. Basilar artery of newborn female. Magnification approximately × 200. Note fibroelastic cushion developing at mouth of a branch at A. Note also absence of external elastic lamella.



3 4

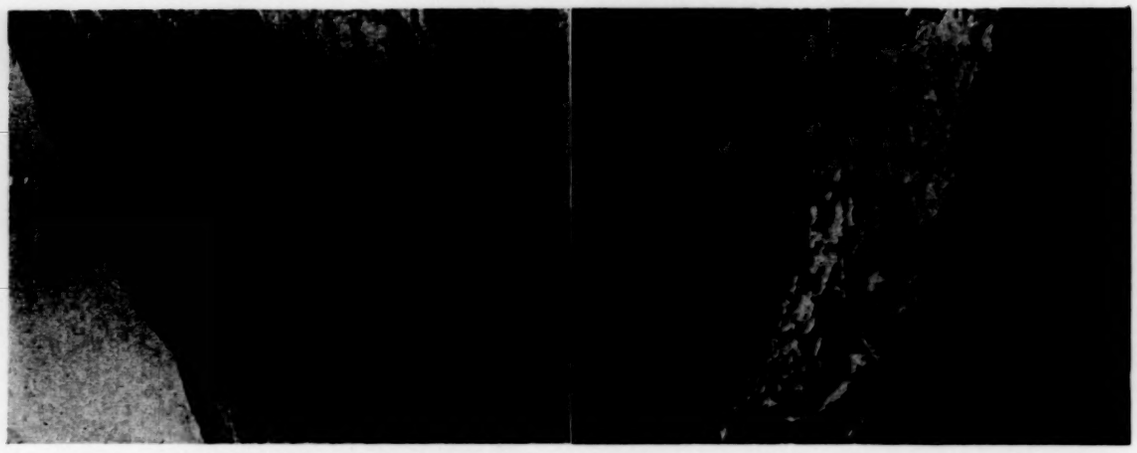
FIG. 3. Basilar artery of thirty-seven year old man. Magnification approximately × 480. Note straight, thick character of internal elastic lamella and loss of beading. Note also absence of elastic elements in media and adventitia.

FIG. 4. Basilar artery of fifty-six year old woman. Magnification approximately × 480. Note gap in internal elastic lamella at point A where intima is hardly thickened. Gap is filled in by fibrous tissue. No elastic elements are present in media or adventitia.

Age Group 20–39 Years (*Thirty-six Cases*). In this age group the depth of the intima varied from 0 to 10 per cent of the thickness of the wall. Focal fibroelastic masses in excess of this thickness were present in nine cases. These showed numerous reduplications of the elastic elements between which there was basophilic ground substance and fibroblasts; no lipid deposits were seen. Beading of the intact internal elastic lamella was observed in eleven instances. In most cases there were wide areas in which the internal elastic lamella presented a straight, intact, plump appearance. (Fig. 3.) Calcification along the latter varied from 0 to less than 1 plus. Where reduplication of elastic elements was seen, calcification was generally 1 plus; when distinct fibroelastic cushions were found, incineration generally revealed slightly more intense calcification.

Fine elastic filaments were seen in the media in seven cases. In general, medial muscle was well preserved even under intimal cushions. Fine elastic filaments were present in sixteen cases in the usual location of the external elastic lamella, and these showed calcification of less than 1 plus. In no instance was a distinct external elastic lamella encountered.

Age Group 40–59 Years (*Twenty-nine Cases*).



5A 5B

FIG. 5. Basilar artery of fifty-nine year old woman. Magnification approximately × 480. A, a large plaque containing elastic elements at surface; base in the intermediate area occupies about 90 per cent of the thickness of the wall. The thin strip devoid of elastic elements along the right margin at A represents the markedly thinned media. Plaque shows lipid spaces near its base. B, microincinerated preparation showing marked deposition of calcium in plaque area.

The depth of the intimal layer varied from 0 in some cases to as much as 30 per cent of the thickness of the wall in others. The internal elastic lamella consisted of a plump straight band extending over wide areas but with interspersed foci of reduplication. Fraying and granulation were less than we have observed in some other arteries. Gaps in the internal lamella had squared edges and were completely devoid of elastic elements; these were not always due to pressure atrophy from overlying plaques since they were even encountered in foci where the intimal layer consisted of as little as 10 per cent of the thickness of the wall. (Fig. 4.) Persistence of beading of the internal elastic lamella was found in two cases. True plaque formation consisting of focal thickening of the intima in excess of 30 per cent of the thickness of the wall was found in fifteen cases. Many of the plaques showed intense reduplication of elastic elements with fraying and moderate granulation; between elastic filaments, fibroblasts and basophilic ground substance were scattered. These plaques produced marked compression atrophy of the underlying media, and in the most severe instances the base of the plaque rested almost on the adventitia. (Fig. 5A.) Plaques with a depth in excess of 50 per cent of the thickness of the wall also contained lipids in varying quantities. However, it is noteworthy that many plaques which presented a yellow gross appearance showed relatively few lipid-containing macrophages or cholesterol crystal deposits. "Aortification" of the wall similar to that observed in the coronary and renal arteries was seen in only one case in this entire series and occurred in this age group. Calcification of elastic elements ranged between 1 and 2 plus, and between 3 and 4 plus in plaques. (Fig. 5B.) Fine filaments of elastic tissue in the media were seen in only two cases (Fig. 6A) and these showed 2 plus calcification. (Fig. 6B.) Likewise, only two cases showed filaments in the position of the external elastic lamella.

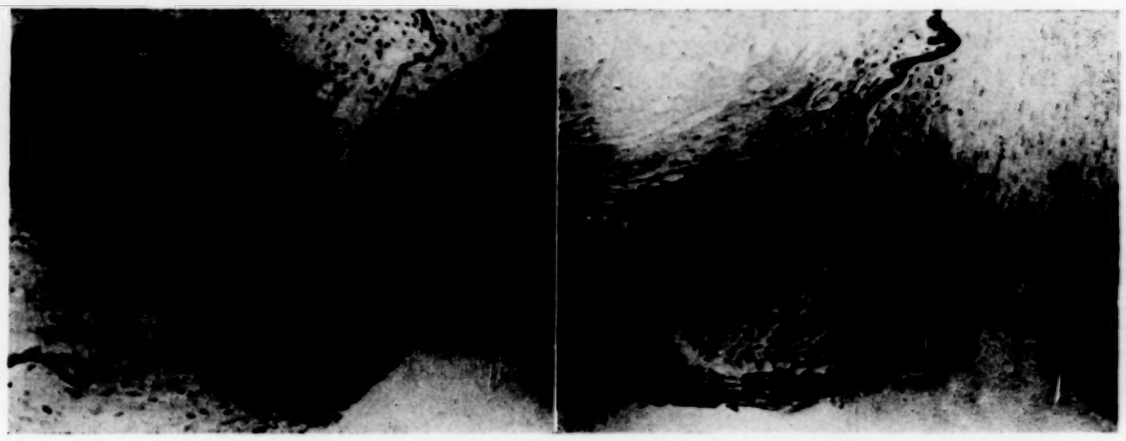
Twenty-three of the specimens in this age group were obtained from hypertensive individuals, and in sixteen of these death was due to cerebrovascular thrombosis or hemorrhage. Plaque formation was most intense in these cases, particularly in the two individuals aged forty-three and forty-five with malignant hypertension.

This was the only age group in which there was a sufficient number of Negro cases with which to make an adequate racial comparison. Elastic tissue calcification was, on the average, more intense in the Negro than in the white group; however, the frequence of plaque formation was about the same.

Age Group 60–79 Years (Forty-two Cases). The depth of the intimal layer varied between 5 and 30 per cent of the thickness of the wall. Reduplications of the internal elastic lamella occurred with only slightly greater frequency than in the previous age group, as did gaps devoid of elastic elements in areas where there was a single thick internal elastic lamella. Beading of the internal lamella persisted in five cases. In addition, ghost

6A 6B

FIG. 6. Basilar artery of forty-five year old man. Magnification approximately × 480. A, note particularly black elastic fibrils in media and a few along adventitia. Internal elastica remains thick, but focal reduplications representative of early plaque formation are present. B, microincinerated preparation shows typical calcification of elastic elements.



7 8

FIG. 7. Basilar artery of sixty-seven year old man. Magnification approximately × 480. Internal elastica remains intact under a large plaque. Note lipid vacuoles in plaque as well as in media. At A internal elastica shows beading and at B it shows a "ghost" characteristic, with loss of affinity for elastic stain.

FIG. 8. Basilar artery of seventy-three year old man. Magnification approximately × 480. Note break in internal elastica produced by penetration of a large atheromatous plaque.

structures were found which presented the configuration and thickness of intact lamella but which had lost their affinity for the elastic tissue stain. (Fig. 7.) Eighteen of the cases showed plaque formation with characteristics similar to those observed in the previous age group. Calcification of elastic elements averaged 2 plus in the white and 3 plus in the Negro group. Within plaques calcification was generally 3 to 4 plus in both groups. Atrophy of the medial muscle occurred beneath large plaques, and in many instances the latter rested directly on the adventitia. Several cases with severe plaque formation showed an inflammatory reaction consisting of fibroblasts and mononuclear cells beneath and along the lateral margins of plaques. Occasionally the elastic elements failed to confine the lower limits of the plaque; their rupture resulted in the extension of lipids into the medial muscle. (Fig. 8.) However, lipids were also seen in the media beneath plaques with apparently intact elastica across the base. (Fig. 7.) Fine elastic filaments were found in the media in five cases and these showed only 1 to 2 plus calcification. Elastic filaments in the location of the external elastic lamella were observed in seven cases.

A history of hypertension was obtained in fourteen cases; six of these patients died of

cerebrovascular thrombosis or hemorrhage. The cases of hypertension generally showed more severe plaque formation than the others in this age group, and calcification of elastic elements was more intense.

Age Group 80 Years and Over (Ten Cases). There was no essential difference between this and the previous age group. Intimal depth varied between 5 and 30 per cent of the thickness of the wall. Plaque formation was found in seven cases. No instances of beading of the internal elastic lamella were seen, but several showed ghost lamellas. Calcification of elastic elements averaged almost 3 plus and ranged between 3 and 4 plus in plaques. Atrophy of the media beneath plaques was common and in three cases the latter rested directly on the adventitia. Elastic filaments in the media were seen in two cases but none were found in the adventitia. Inflammatory reaction adjacent to plaques was seen in one case.

A history of hypertension was present in six patients, two of whom died of cerebrovascular thrombosis. These two cases showed the most intense plaque formation in this age group.

TABLE II

EFFECTS OF HYDROSTATIC TENSION AND AGE ON THE WALLS OF CEREBRAL ARTERIES

Artery	Age Group (yr.)	Number Measured	Average Internal Radius (cm.)	Tension* (dynes/cm²)	Average Wall Thickness (mm.)	Frequency of Plaque Formation (%)
Internal carotid	23–45	24	0.066	6,864	0.26	12.5
	46–93	50	0.087	9,048	0.51	46.0
		Av. dilation† 31%			Av. increase‡ 96%	
Basilar	23–45	11	0.063	6,552	0.20	0
	46–93	26	0.081	8,424	0.54	50
		Av. dilation 27%			Av. increase 170%	
Middle cerebral	23–45	24	0.054	5,616	0.18	12.5
	46–93	52	0.065	6,760	0.42	50
		Av. dilation 20%			Av. increase 133%	
Vertebral	23–45	16	0.054	5,616	0.18	0
	46–93	42	0.064	6,656	0.42	43
		Av. dilation 19%			Av increase 133%	
Posterior cerebral	23–45	23	0.038	3,952	0.18	4.3
	46–93	46	0.052	5,408	0.35	39.1
		Av. dilation 37%			Av. increase 94%	
Anterior cerebral	23–45	23	0.038	3,952	0.15	0
	46–93	52	0.048	4,992	0.20	17.3
Anterior communicating	23–45	8	0.033	3,432	0.15	0
	46–93	17	0.045	4,680	0.18	6
		Av. dilation 36%			Av. increase 22%	
Posterior communicating	23–45	13	0.027	2,808	0.14	0
	46–93	23	0.032	3,328	0.15	4
		Av. dilation 18%			Av. increase 7%	
Superior cerebellar	23–45	16	0.023	2,392	0.14	0
	46–93	33	0.026	2,704	0.15	0
		Av. dilation 13%			Av. increase 7%	

* Calculated from the Laplace equation: Tension = Mean Pressure × Radius.
† Percentage increase in radius of older group over younger group.
‡ Percentage increase in thickness of older group over younger group.

Relation of Hydrodynamic Tension to Gross Anatomic Changes in Cerebral Arteries

Some interesting data derived from the measurements of arterial walls are shown in Table II. The various arteries of the circle of Willis have been arranged in order of diminishing internal radius and hence also in order of decreasing hydrostatic tension. From a comparison of the average internal radius in the two age groups a figure for average dilation has been derived, and this varied between 13 and 37 per cent. On the other hand, a similar comparison of the increase in average wall thickness with age showed a

variation between 7 per cent in low tension and 170 per cent in high tension arteries. These data are interpreted as indicating that the increase in wall thickness tends to maintain a relatively constant internal diameter of the artery wall. However, this mechanism is an imperfect one, and the degree to which a vessel dilates determines the increase in hydrostatic tension with advancing age. Further, the differences in hydrostatic tension between larger and smaller arteries are probably somewhat greater than recorded in Table II, since these calculations have been made on the basis that the same pressure obtains in all major arteries of the circle of Willis whereas it probably diminishes as the arteries become smaller.

As in the previous study with arteries of the lower extremity,[18] the frequency of plaque formation was, in general, greatest in those arteries operating at high hydrostatic tensions. The one possible exception is the internal carotid artery which showed a relatively high incidence of plaque formation but not as high as in some other arteries operating under somewhat lower tensions; general thickening of the wall of the internal carotid was also not as great as in the latter. A possible explanation for this discrepancy is presented in the discussion.

A surprisingly large number of gross anomalies were encountered in the thirty-seven circles of Willis examined. These are listed in Table III. Their possible relation to sites of formation of plaques will be discussed.

As has been noted by many observers in studies dealing with arteriosclerosis, the earliest intimal plaques occur at or near the mouths of branches. This is also true of the arteries composing the circle of Willis (Figs. 9 and 10) even in the instance of the fibroelastic cushions of the newborn. (Fig. 2.) The significance of such observations in a mechanical concept of arteriosclerosis is considered in the discussion.

DISCUSSION

It has already been mentioned that cerebral arteries differ structurally from those elsewhere in the body, and that the absence of certain structures might be expected to intensify the arteriosclerotic process if the development of the latter is dependent upon the action of physical forces. These structural differences were first reported by Triepel[22] in 1897. He observed that cerebral arteries differed from similar-sized vessels elsewhere in the greater prominence of the internal elastic lamella, in the slight development of elastic tissue in the medial coat and in the striking decrease in elastic fibers in the adventitia. The present report confirms these observations in all essential respects. Despite such apparent vulnerabilities and their possible significance in the genesis of cerebral arteriosclerosis, only one comprehensive study of the latter disease appears in the medical literature (Wolkoff[24]).

TABLE III
ANOMALIES OF THE CIRCLE OF WILLIS

	Number	
Absent superior cerebellar artery	2	
Multiple anterior cerebral arteries distal to level of anterior communicating artery	2	
Atresia or absence of first order branch:		
One or both posterior communicating	5	
Right posterior cerebral	1	
Anterior cerebral (distal portion)	1	7
Single anterior cerebral artery originating from anterior communicating artery	1	
Combined origin of posterior cerebral and superior cerebellar arteries	2	
Origin of second order bifurcations close to first order division	4	
		18 (48.6%)

The internal elastic lamella of the basilar artery is not only more prominent than in other arteries of corresponding size but also shows a peculiar beading which we have not observed elsewhere. This configuration of the elastica persists through the seventh decade of life in some individuals, although it has been observed with diminishing frequency as age progresses. Careful study suggests that the apparent beading is not a true polypoid projection but is due rather to a tighter configuration of the normal wavy structure characteristic of the elastica interna in the unextended state. The diminishing frequency with increasing age therefore probably results from stretching of the inner elastic band incident to dilation of the artery.

The internal elastic lamella of the basilar artery presents further characteristics not observed elsewhere. Sharply demarcated gaps in which there appears to be a complete absence of elastic elements have been noted frequently after the age of fifty, but were also found in one patient twenty-nine years old. The development of such defects is not necessarily a complication of pressure from an overlying intimal plaque since they have been observed frequently in areas showing only minimal intimal thickening. (Fig. 4.) They are frequently but not always

9 10

FIG. 9. A forty-three year old woman. Magnification approximately × 4.5. Figure shows superior cerebellar and posterior cerebral arteries emanating from the basilar artery. A plaque is forming at the site of origin of these branches.

FIG. 10. A sixty-seven year old man. Magnification approximately × 4.5. Two points of bifurcation in first order branches of the circle of Willis. Note extensive plaque formation near origins of bifurcations as compared with more distal portions.

associated with underlying medial fibrosis. Such gaps have also been observed by Carmichael[6] who thought they might result from focal erosion of overlying atheromatous degeneration. Their sharp demarcation suggests sudden rupture of the internal elastic lamella at some focal point with subsequent lateral retraction. A subsequent report dealing with cerebral artery aneurysm formation on an inflammatory basis will present evidence for focal weakening of the internal elastica, at least in some instances, by inflammatory reaction.

Occasionally we have observed "ghosts" of the internal elastic lamella (Fig. 7) characterized by a focal loss of affinity for the elastic tissue stain. The etiology of this alteration remains obscure, although this may be a stage of atrophy of elastic tissue which has also been noted previously in the wall of the aorta.

Reduplication, fraying, fragmentation and granulation of the internal elastic lamella occurs in the basilar artery as in arteries of comparable size elsewhere. However, the intensity of these changes is slightly less than in arteries elsewhere in the body in corresponding age groups, and coincidental calcification, as observed in micro-incinerated sections, is also slightly less intense. This is probably due to the fact that the thicker internal elastic membrane in cerebral arteries may be somewhat more resistant to wear and tear effects than elsewhere. Furthermore, true "rock" and bone formation along the internal elastica in the absence of plaques was not observed; thus far we have seen the latter development only in those arteries which respond readily by constriction to epinephrine. While epinephrine can constrict cerebral arteries, Schmidt[21] points out there is general agreement that the effect on cerebral vessels is much weaker than on vessels elsewhere. However, "rock" formation along the elastica interna was occasionally observed at the base of large atheromatous plaques in the basilar artery.

We were able adequately to compare the intensity of the foregoing changes, as well as intensity and frequency of plaque formation, on a racial basis in only one age group (forty to fifty-nine years) because of the limited number of Negro cases. In this group these alterations were on the average moderately more intense in Negroes than in white individuals.

It is generally assumed that the intima is a normal structural component of an artery. However, all arteries which we have studied thus far, both of the systemic and pulmonary circulation, are initially without such a layer. Arteries of the newborn have invariably shown the internal elastic lamella in contact with the endothelial lining on one surface and with medial muscle on the other. The intimal layer develops subsequently, and with advancing age becomes progressively thicker. In most instances it consists of fibroblasts, collagen, basophilic ground substance and elastic fibrils. Noteworthy

is the absence of lipids for a long period of time. Over large areas the intima shows a uniform progressive thickening and may produce marked concentric narrowing of the lumen of sufficient degree to obstruct as effectively as eccentric plaques. Apparently because of local mechanical or structural conditions, the intima may thicken more rapidly in one area, giving rise to plaque formation. Characteristically the latter occurs at mouths of branches but may subsequently spread laterally or, in advanced cases, appear in other foci.

This concept of the sequence of events in the formation of an intimal plaque has been derived from a careful study of various arteries of the human circulation arranged according to age. Assuming uniform intensity of mechanical forces in all cases, the intensity and frequency of plaque formation would be expected to increase with time, and the intensity of arteriosclerosis would therefore increase with chronologic age. On the whole this is true; exceptions occur when the intensity of physical forces is increased, as illustrated by the increased severity in hypertensive individuals in the present series, or when local situations of susceptibility in the form of structural weaknesses occur. Moschcowitz[17] has expressed this idea in the phrase "no intravascular pressure, no arteriosclerosis."

On the other hand, certain vessels are capable of developing structural responses which have a protective effect and delay the formation of intimal plaques. "Aortification" of coronary and renal arteries, marked calcification of the external elastic lamella of the renal artery and the outer half of the media of the splenic artery, and calcification and bone formation along the internal elastic lamella in arteries which show a marked vasoconstrictor response to epinephrine may be examples of such a phenomenon.

The cerebral artery is, however, an excellent example of increased susceptibility to plaque formation because of certain inherent structural weaknesses. The latter include a relative lack of potentiality for developing elastic fibers in the media and adventitia, and the existence of, at best, only a rudimentary external elastic lamella. Furthermore, those elastic fibrils which are present in the media and adventitia apparently diminish with advancing age. The susceptibility of this segment of the arterial circulation is best exemplified in the formation of plaques in some instances even before birth. Tuthill,[23a] Hackel,[11] Ruehl[20] and Beneke[1] have each described fibroelastic cushions of cerebral arteries at the site of formation of branches. They have been found in the human fetus of seven months' gestation and apparently remain histologically unchanged until after the age of twenty (Hackel[11]). The only explanation offered for their existence has been presented by Beneke[1] who observed them at bifurcations of meningeal arteries and attributed their development to pulse force. The occurrence of these fibroelastic cushions lends further support to the concept offered by us and by Moon and Rinehart[16] that the deposition of ground substance, fibroblasts, collagen and elastic elements precedes the occurrence of lipids in atheromatous plaques.

A further characteristic of arteriosclerosis of the basilar artery, and very likely of other cerebral arteries, is the tendency of the plaque to extend into the media as much as to project into the lumen and thereby eventually to rest on the adventitia. This is due not only to structural weaknesses but also to a relative lack of potentiality for new formation of elastic elements characteristic of other arteries. Such lack of support and the resulting penetration of plaques very likely accounts for the considerably higher incidence of rupture and aneurysm formation on an arteriosclerotic basis in cerebral arteries than elsewhere. We are not in agreement with Duff and McMillan[7] that atherosclerosis affects the cerebral arteries later in life than the aorta and coronary arteries.

From the data presented in Table II it is apparent that the dilating effect of hydrostatic tension results in a thickening of the arterial wall; this process limits the increase in internal radius and thereby also limits the increase in hydrostatic tension with advancing age. The intensity of this response correlates well with the magnitude of the tension in various locations. From the microscopic studies it is evident that this increased thickness is primarily due to a progressive increase in the intimal layer. While the intensity of the latter process correlates well with the frequency of plaque formation, it does not explain the predilection of the latter for certain foci, namely, the mouths of bifurcations. Several possibilities deserve investigation in this regard: (1) These areas may be structurally weaker than uninterrupted portions of the arterial tube; (2) tension may not be equally distributed along all portions of the tube but may be greater at division points; and (3) certain characteristics of the flow pattern at points

of bifurcation may introduce other factors of a traumatic nature.

Regarding the first of these possibilities, Forbus,[8] Glynn,[9] Carmichael[6] and others have described muscle defects at points of bifurcation of cerebral arteries. While the relation of these to the formation of aneurysms has been disputed, most observers except for Tuthill[23b] accept the validity of this observation. More pertinent perhaps is the observation of Triepel[22] that as cerebral arteries decrease in size, the elastica interna progressively decreases in thickness until it finally disappears entirely in the precapillary stage. Since branches are generally of smaller diameter than the parent artery, and their operating tensions therefore also smaller, it is possible that the effective tension at the mouths of bifurcations is that of the parent artery while the structure on which it acts is the weaker one of the branches. The great variability in arrangement and size of the various components of the circle of Willis, as previously noted, may in some instances operate to intensify such an effect.

Forbus' report[8] also contains observations pertinent to the second possibility. From observations on artificially constructed rigid tubes forming bifurcations at several angles, he concluded that the pressure within such systems is not exerted equally in all directions but is greatest at a point opposite the axis along which the pressure is applied, the carina of a bifurcation. It should be pointed out, however, that these observations were made on rigid rather than pulsating tubes and with constant pressure rather than one fluctuating between systolic and diastolic levels.

As regards the third possibility, analysis of vibration and shearing effects at divisions, particularly in relation to the angle of bifurcation, is certainly in order, as is that of effects of eddies and currents. These subjects are being considered for future investigations.

Finally, as regards localization of plaques Ranke[19] has pointed out the relation of adjacent bony structures, particularly with respect to the aorta and spinal column, to the distribution of atheromas. A similar situation obtains as regards the internal carotid artery as it passes through the base of the skull. Where arteries are in contact with bony structures, the intensity of plaque formation is usually increased. However, in the case of the internal carotid artery our results indicate that plaque formation may be less intense distal to the point where the vessel emerges from the base of the skull, and is less marked than in arteries somewhat smaller in size. Although the latter difference may not be significant, we plan to pursue this problem further and to investigate the possibility of a carotid sphincter which may operate to protect not only the distal segment of that artery but also that portion of the circle of Willis which directly receives carotid blood. At the suggestion of Dr. J. Edwards of the Mayo Clinic, one of us (F. P. H.) has identified, with selective stains, smooth muscle bundles in the adventitia of the external iliac artery beyond the external lamella which may act as such a sphincter.

This investigation therefore emphasizes again the importance of mechanical factors in the genesis of arteriosclerosis and indicates that certain structural weaknesses in the circle of Willis tend to intensify the effects of such factors. Present observations support the concept that the alterations in arteries which lead to the development of arteriosclerosis are of an adaptive nature which tend to minimize the increase in internal diameter produced by hydrodynamic factors acting over long periods of time. While the predilection of certain sites for plaque formation is not fully accounted for, certain areas of investigations are indicated for further clarification of this aspect of the problem. Also indicated are investigations dealing with the relation of physical forces to biochemical processes, since it is apparent from our observations that mechanical factors act to stimulate the new formation of certain tissue elements, and the breakdown of other structures with local release of metabolites, particularly lipids, which may remain in the vessel wall.

SUMMARY

The histogenesis of cerebral arteriosclerosis has been studied in the basilar arteries of 124 patients ranging in age from newborn to ninety-three years. This has been supplemented by gross examination of thirty-seven circles of Willis in which locations of plaques have been mapped, internal and external diameters measured, and vascular anomalies recorded.

It has been shown that the differences in histologic pattern of development of arteriosclerosis in the basilar artery from patterns observed elsewhere are in large part determined by certain inherent weaknesses of the wall characteristic of cerebral arteries and accounting for

the considerably higher incidence of aneurysm and rupture than occurs elsewhere.

Measurements of the internal and external diameters of arteries have permitted calculation of effective hydrostatic tensions in various locations in the circle of Willis. The calculated tensions have been correlated with degrees of dilation and thickening of the wall with age, and with the frequency of plaque formation.

From such data and the histologic studies, a concept has been derived that arteriosclerosis is fundamentally an adaptive response, structural as well as biochemical, to mechanical factors, in which all layers of the arterial wall are involved. Some of the physical factors are of general type, others local in character.

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Blood Lipid Levels As Influenced by Weight Reduction in Women*

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REPORTS are not in agreement regarding the influence of weight reduction on blood lipids, notably cholesterol. Poindexter and Bruger[1] studied the changes in plasma cholesterol levels (mostly non-fasting values) in thirty subjects undergoing weight reduction on low calorie diets, over periods ranging from six to sixty weeks. Fourteen of the subjects had uncomplicated obesity, the others were afflicted with some metabolic disease. For a given subject, the cholesterol values fluctuated considerably over the experimental period but the data as a whole revealed no changes attributable to weight reduction in either group. Walker and Weir[2] reported a short-time study of twenty-seven obese subjects who underwent rapid weight reduction by rigid calorie restriction (600 to 800 calories per day). Most patients lost 4 pounds per week. The diet was extremely low in fat (11 gm. per day) and relatively high in protein (82 gm.). Based on determinations which were made prior to weight reduction and from one to three times during the three or four weeks' period of observation, the plasma cholesterol values, while showing considerable fluctuations for the individuals, were considered to indicate a downward trend.

More recently Walker et al.[3] reported a longer term study of the effect of weight reduction, by means of a 1,000 calorie diet containing 100 gm. protein, 50 gm. fat and 600 mg. cholesterol, on serum lipoproteins and cholesterol levels in thirty-nine male and female subjects, twenty-nine of whom were known to have cardiovascular disease. Blood samples were taken every two or three weeks but in no constant relationship to meals. It is reported that after weight losses of 7 to 40 pounds serum cholesterol levels decreased in the majority of subjects. However, those who lost weight rapidly and those losing the greatest amounts showed less change in serum cholesterol level than did those losing more slowly or in smaller amounts. Thus it was considered inconclusive whether weight reduction *per se* or the relatively low fat intake was responsible for the decrease in serum lipids observed.

Young et al.[4] measured the nitrogen, calcium and phosphorus metabolism of six college women who lost an average of 19 pounds in ten weeks on a diet containing 1,400 calories, 80 gm. of fat and 90 gm. of protein, and also obtained data on the levels of total lipids, phospholipids and cholesterol in the blood. On the basis of single determinations the values for all lipids in all subjects were somewhat higher at the close of the reduction period than prior to its start. Slight further increases were recorded four weeks later on a maintenance diet.

The study reported in the present paper was undertaken to obtain further data on the influence of weight reduction on the various blood lipids. Advantage was taken of the opportunity available in the Nutrition Clinic sponsored jointly by the local medical society, the county health department and the School of Nutrition. All patients were informed of required procedures and the importance of regular attendance at the Clinic. Those who indicated unwillingness to participate in laboratory studies were rejected by the screening group for the Clinic. Any defect of which the attending physician was aware was made known to Nutrition Clinic personnel. Previous to reduction each patient kept a diet record of all food intake for one week and an activity record for three typical days. Each patient was requested to eat normally and carry on her usual activity during this period. Data from these records were computed for calories consumed and calories expended in

* From the School of Nutrition, Cornell University, Ithaca, N. Y. Supported in part by an appropriation from the State of New York through the State University and in part by a grant from the Nutrition Foundation, Inc., New York, N. Y.

TABLE I*

Patient No.	Rate of Weight Loss (pounds/wk.)	Total Lipids/mg. per 100 cc.				Phospholipids/mg. per 100 cc.				Cholesterol/mg. per 100 cc.			
		Initial	Terminal	Highest	Lowest	Initial	Terminal	Highest	Lowest	Initial	Terminal	Highest	Lowest
30	1.98	455	643	725	525	220	300	340	200	188	257	289	188
97	1.49	800	595	800	540	280	263	280	225	226	228	228	189
58	1.46	†	435	540	435	182	185	220	182	149	152	172	149
106	1.42	765	760	788	555	340	295	340	242	285	248	285	215
51	1.30	450	465	525	450	213	205	258	197	184	159	196	159
75	1.28	634	475	634	454	283	250	283	208	222	208	222	172
27	1.12	675	625	675	610	318	278	318	253	245	251	263	242
109	1.0	737	868	908	590	303	373	358	263	269	275	288	244
92	1.0	572	554	572	450	220	248	255	188	166	190	190	162
23	0.96	455	400	455	365	175	183	183	145	167	170	170	125
102	0.91	450	640	640	450	205	273	273	197	200	210	219	178
116	0.89	535	554	554	440	215	238	238	178	172	183	183	155
6	0.88	700	710	726	615	303	340	340	280	246	284	284	245
57	0.85	525	509	525	415	210	232	232	200	190	185	190	167
61	0.84	620	540	620	460	265	292	292	228	203	214	234	192
41	0.84	792	535	792	440	250	235	267	203	204	204	219	164
13	0.84	690	†	787	630	343	†	348	270	249	255	288	227
53	0.76	575	725	725	535	248	283	283	210	229	292	292	190
44	0.76	817	690	870	690	313	295	363	270	285	250	337	250
100	0.73	650	845	845	650	253	315	338	253	235	335	335	235
65	0.71	665	890	890	645	245	353	353	245	214	330	330	214
18	0.66	515	500	540	500	195	212	250	195	184	213	213	182
93	0.63	675	610	720	610	262	303	318	262	208	239	270	208
35	0.60	825	750	825	535	298	270	298	250	237	209	245	197

* Serum lipid values in twenty-four women who lost weight. Subjects are arranged in order of rate of weight reduction.

† Values not obtained.

TABLE II*

Patient No.	Rate of Weight Change (pounds/wk.)	Total Lipids/mg. per 100 cc.				Phospholipids/mg. per 100 cc.				Cholesterol/mg. per 100 cc.			
		Initial	Terminal	Highest	Lowest	Initial	Terminal	Highest	Lowest	Initial	Terminal	Highest	Lowest
89	0.46	590	617	617	574	247	250	275	249	207	215	215	198
12	0.44	675	610	786	475	250	285	300	205	209	189	246	180
98	0.26	700	615	735	600	270	288	288	263	214	224	235	214
67	0.25	820	755	925	755	267	280	292	267	235	225	251	208
47	0.22	720	920	920	690	227	350	350	227	200	324	324	200
29	0.16	660	585	758	585	248	255	278	218	211	233	250	211
84	+.11	590	680	680	475	250	278	278	250	215	256	256	198
22	+.18	745	791	791	710	255	310	322	255	242	258	258	204
72	+.25	675	565	675	565	292	270	292	188	215	213	252	211
103	+.32	518	645	645	504	220	315	315	220	140	217	217	140
48	+.35	465	510	520	465	165	215	220	165	139	164	184	139
14	+.40	820	705	820	705	320	280	323	280	294	279	294	245

* Serum lipid values in twelve women who did not lose appreciable weight. Patients are arranged in order of rate of weight change.

twenty-four hours. During the pre-dieting week a fasting blood sample was obtained for total serum lipids, serum cholesterol and serum phospholipids. Blood determinations were repeated at approximately monthly intervals. During the second visit to the Clinic patients gave a weight and medical history; past illness or other factors which may have contributed to the patient's overweight were included. After these procedures were completed the nutritionist gave each patient the diet to be followed.

The level of fat in the diet varied from 50 to 80 gm. per day among subjects. Inasmuch as a moderate fat diet was being studied for its satiety value, nearly half (eleven of twenty-four) of the patients had prescriptions of the order of 80 gm. fat, 90 gm. protein and 80 gm. carbohydrate. For the other 13 patients fat intake varied between 50 and 65 gm. per day with a mean of 56.5 gm. and a median of 55. The percentage of estimated caloric intake derived from fat ranged from 35 to 50 per cent, with a mean of 45 and a median of 47 per cent.

This paper deals with repeated observations on blood lipid levels of twenty-four women sixteen to sixty-six years of age while losing weight for approximately six months at a rate varying from 0.6 to 2 pounds per week, or a total weight loss varying from 16 to 59 pounds. A brief discussion is also given of comparable observations on the blood lipid levels of twelve other female subjects thirteen to fifty-nine years of age who were not successful in weight reduction because of failure to follow the prescribed diet.

The data for total lipids here presented represent the combined total fatty acids and cholesterol as determined by the method of Bloor.[5] The phospholipids were obtained by determining phosphorus in the lipid extract by the method of Sumner.[6] The total and free cholesterol were obtained by the method of Sperry and Webb.[7]

RESULTS

Total Serum Lipids. Of the twenty-four subjects who lost weight, initial and terminal serum lipid values in twenty-two are presented in Table I. Thirteen subjects had a terminal value lower than the initial one and nine had higher terminal values. However, ten of the subjects had a change of less than 10 per cent in serum lipid levels. Of those with changes greater than 10 per cent, six had terminal values higher than initial ones and six subjects had lower terminal values. The same pattern prevailed when the twenty-two patients were divided into groups which lost weight at rate of 0.6 to 1 pound and 1 to 2 pounds per week.

The trends indicated by the initial and terminal values were subject to wide variation in intermediate values as indicated by the data for the highest and lowest values in Table I. Among individuals, the range of variation over the period showed deviations of 8 to 65 per cent from their means. Wide fluctuations occurred regardless of rate of weight loss.

In Table II initial and terminal serum lipid values are given for twelve overweight women whose weight changed but little over the observation period and who will be called controls. Six lost weight varying from 5 to 14 pounds at a rate varying from 0.2 to 0.5 per week and six gained slightly, 2 to 7 pounds at a rate varying from 0.1 to 0.4 pound per week. Of this group six subjects showed terminal total lipid values higher and six showed lower terminal values. This was also true of those of this group who had differences greater than 10 per cent. Individual variations of total serum lipid values among the control group during the observation period varied from 7 to 50 per cent from their means.

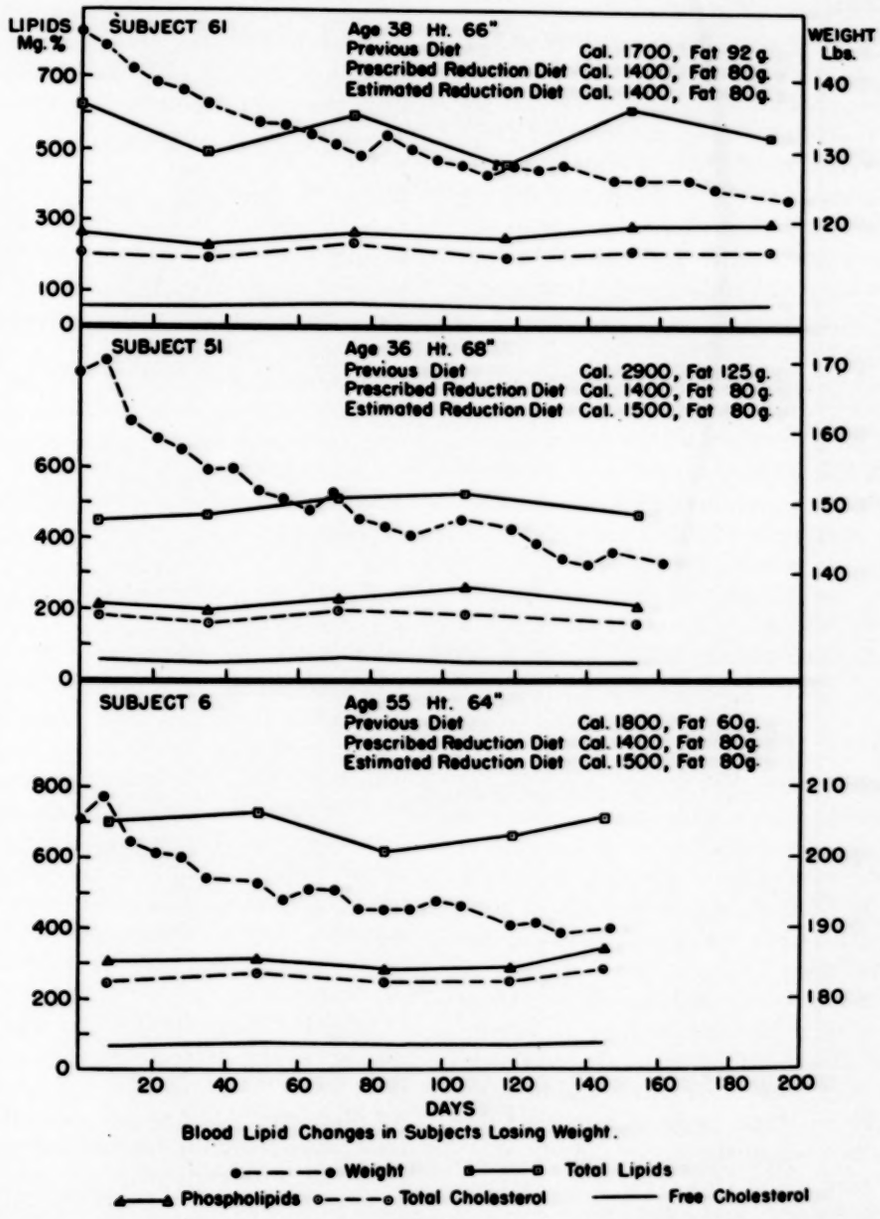
A covariance analysis shows that there is no detectable linear relation between weight change and level of total serum lipids within individuals.

Phospholipids. Phospholipid data are presented in Table I for twenty-four subjects losing weight. In the case of one subject no terminal value was obtained. Fifteen subjects ended the weight reduction period with phospholipid levels above their initial levels and eight subjects had lower terminal levels. If only those who had differences above 10 per cent are considered, ten had higher terminal phospholipid values and three lower values. Of the sixteen who lost weight at rates of 0.6 to 1 pound per week, thirteen had terminal phospholipid serum levels higher than initial values and three lower. By contrast, of those who lost weight at rates of 1 to 2 pounds per week, the majority had lower terminal phospholipid levels. During the weight reduction period there were serum phospholipid variations among individuals of 15 to 55 per cent from their means in the group of twenty-four subjects who lost weight. The range of variation was the same irrespective of rate of weight loss.

Of the twelve control patients in Table II, ten

had higher levels of phospholipids at the end of the observation period and two had lower levels, a similar picture for the group losing weight. The results were similar whether the differences were greater or less than 10 per cent. Variations among individuals ranged 8 to 40 per cent from their means in serum phospholipid levels.

A covariance analysis* shows that there is a small significant over-all linear relation within individuals between weight loss and phospholipids. This relation was significant at the 5 per cent level. The average regression coefficient of −.64 indicates that on the whole there is an increase within individuals of 0.64 mg. of serum phospholipids for each pound of weight lost.


LIPIDS Mg.%
WEIGHT Lbs.
SUBJECT 61
Age 38 Ht. 66"
Previous Diet Cal. 1700, Fat 92 g.
Prescribed Reduction Diet Cal. 1400, Fat 80 g.
Estimated Reduction Diet Cal. 1400, Fat 80 g.
SUBJECT 51
Age 36 Ht. 68"
Previous Diet Cal. 2900, Fat 125 g.
Prescribed Reduction Diet Cal. 1400, Fat 80 g.
Estimated Reduction Diet Cal. 1500, Fat 80 g.
SUBJECT 6
Age 55 Ht. 64"
Previous Diet Cal. 1800, Fat 60 g.
Prescribed Reduction Diet Cal. 1400, Fat 80 g.
Estimated Reduction Diet Cal. 1500, Fat 80 g.
DAYS
Weight
Total Lipids
Phospholipids
Total Cholesterol
Free Cholesterol

Blood Lipid Changes in Subjects Losing Weight.

FIG. 1.

Cholesterol. In Table 1 data showing serum cholesterol levels for twenty-four subjects are presented. Seventeen subjects had terminal serum cholesterol levels higher than the initial ones; six had lower values and one was unchanged. Of the twelve subjects who had more

* The authors are indebted to Drs. R. G. C. Steel and F. E. Hobson of the Biometrics Unit, Department of Plant Breeding, for statistical analysis of total serum lipid, phospholipid and cholesterol data.

than a 10 per cent difference between the initial and terminal cholesterol values, eight showed an increase and four subjects had a decrease. Among twenty-four subjects who lost weight individual differences in cholesterol values ranged from 8 to 44 per cent from their means regardless of rate of weight loss.

The data for cholesterol values in the control group show that eight subjects increased their cholesterol levels during the observation period and in four subjects the level decreased during the same period; a picture similar to that shown by the group losing weight. Individual fluctuation of cholesterol levels among the control group during the observation period varied from 8 to 47 per cent from their means, a range of variation similar among those who lost weight.

A covariance analysis* of the cholesterol data showed for the group which lost weight a small over-all linear relation within individuals between weight change and cholesterol. This relation was significant at the 5 per cent level. The average regression coefficient of $-.58$ indicates on the whole an increase within individuals of 0.58 mg. of serum cholesterol for each pound of weight lost.

DISCUSSION

In any discussion of the changes occurring in blood lipid levels during weight reduction it is necessary to consider such factors as the rate of weight loss, the level of fat in the diet, metabolic variables in an individual over periods of time (such as menstruation) and the function of the gastrointestinal tract.

In the three studies referred to earlier[1-3] there was evidence of wide fluctuations in serum cholesterol levels and in two of the studies[2,3] a downward trend was noted with weight reduction, especially in those patients in whom the rate of loss was low. In the present study, also, fluctuations were wide. However, the trends of the serum cholesterol and phospholipid levels were slightly upward with weight loss rather than downward. Our study differed from those of Walker and associates in that the fat intake levels were somewhat higher.

In normal people Man and Gildea[8] noted a similar wide fluctuation in cholesterol, titrated fatty acids and lipid phosphorus levels. In one case, during a weight loss of 27 pounds in one month, or at a rate of loss of 6.7 pounds per week, there was no appreciable change from the serum cholesterol pattern previously shown. In the data presented here there is no significant difference between the group losing at the rate of 0.6 to 1 pound per week from the group losing weight at the rate of 1 to 2 pounds per week, or from the control group.

Examples of variability of serum lipids in weight reduction are given in Figure 1 in which the variability in lipid levels as seen over a six months' period in three typical patients who lost weight is shown. In subject 61 the blood lipids went through a cycle of approximately equal magnitudes about every seventy days. This occurred whether the rate of loss was substantial (first seventy days) or small (last eighty days). If the first forty days only had been recorded, one might surmise that a lowering of blood lipids occurs with weight reduction. If the second forty days had been recorded as the sole observation period, the reverse conclusion could have been reached. While the total serum lipid level fell, and both the cholesterol and phospholipid levels rose during the observation period, there was no relationship to weight loss. Subject 51 shows a similar but less cyclic course of the blood lipids in relation to weight loss. There was no abrupt change in total lipids with reduction in fat intake in the diet from the pre-dieting level and/or the sharp reduction in weight during the first sixty days. There was a slight lowering of the serum phospholipid and cholesterol levels during this period. The last sixty days of this subject's curve shows that all serum lipid levels went down as the rate of weight loss decreased.

Subject 6 illustrates the fact that an increase in diet fat is not necessarily reflected in the blood lipid level. Whereas all serum lipids rose slightly for fifty days, while on the same diet the reverse took place from the fifty-second to the eightieth day. With this patient the serum lipids rose somewhat sharply during the last sixty days in contrast to patients 61 and 51.

The data show no relationship between either level of fat in the diet and changes in serum lipid levels or between the percentage of estimated caloric intake derived from fat and changes in these levels.

That striking and consistent cyclic alterations in the blood lipid content occur within a few days of menstruation is reported by Okey and Boyden.[9] In the present study we have no data

* See footnote on page 351.

relative to the effects of menstruation on the blood lipids in women losing weight. Conceivably it could have affected lipid levels. However, such an effect was not evident. All patients reported normal gastrointestinal function throughout the observation period.

48 gained weight toward the end of the observation period. For 120 days the weight was fairly constant. During both the constant period and the period of increasing weight the lipid levels changed but little. Subjects 67 and 98 show similar serum lipid fluctuation patterns as do

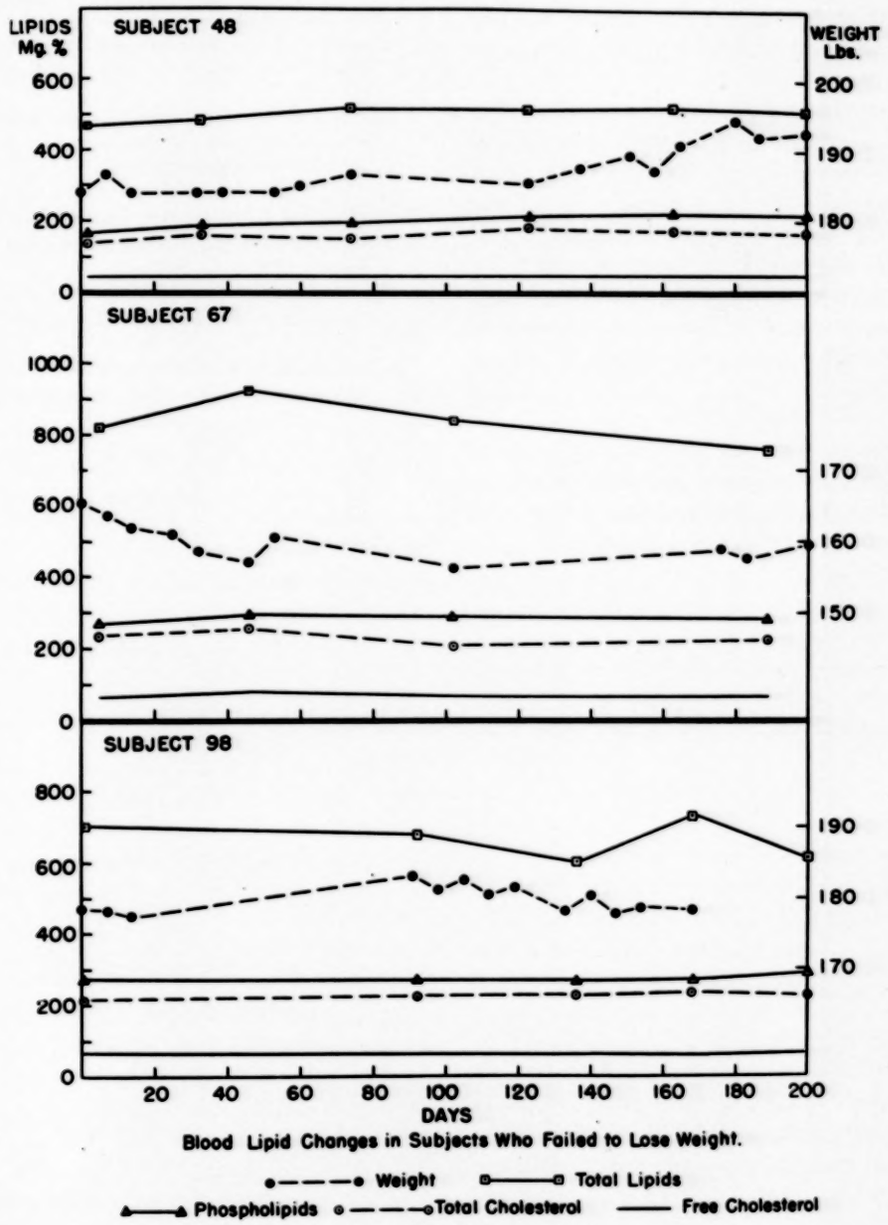


FIG. 2.

Figure 2 shows data for three control subjects, one who gained weight slightly (No. 48); one who lost weight slightly (No. 67); and one whose weight remained the same (No. 98). The fat intakes could not be estimated for any of these three for reasons already mentioned. Subject

those subjects who lost weight at a substantial rate.

SUMMARY

This paper presents blood lipid data for twenty-four women who lost from 15 to 60 pounds in weight at rates varying from 0.6 to

2 pounds per week on diets containing approximately 1,400 calories and 50 to 80 gm. of fat daily. Also, data are presented for twelve women of comparable age who did not lose weight over a similar period of time.

The data as a whole reveal the rather wide fluctuation in blood lipids which occurs in women whether losing weight under dietary control or changing little in weight with no dietary control.

The data provide no support for the view that weight loss is accompanied by a drop in cholesterol or other blood lipids. On the contrary a slight rise was indicated for a majority of the subjects. In the case of serum cholesterol and phospholipids, statistical analyses revealed an increase of 0.58 mg. of cholesterol and 0.64 mg. phospholipid per pound of weight loss for the group losing weight; both were significant at the 5 per cent level.

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Studies on the Adrenal Zona Glomerulosa of Hypertensive Patients and Rats*

With Special Reference to the Effect of Dietary Salt Restriction

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PARTICIPATION of the adrenal cortex in the various types and phases of hypertensive disease is probable. But the mechanisms are not at all clear.[1,2] Hypertensive patients treated with the rice diet offer an opportunity to study certain relationships of the adrenal cortex to hypertension. Their blood pressure is significantly reduced by this treatment in the majority of the cases, frequently returning to normal values.[3,4] It is conceivable that this could be due to decreased activity of the adrenal cortex under the influence of the regimen. Additional factors seem to support this conception, such as the observation of increased sugar tolerance and decreased insulin need in many diabetics who have been treated for their vascular disease with the rice diet,[3] and the general tendency toward serum potassium elevation in patients on the rice diet.[5] On the other hand, in 95 per cent of the patients without severe renal involvement the urinary excretion of sodium is reduced to almost zero, and the serum sodium concentration is maintained.[5] This could mean that the adrenal cortex is functioning optimally in these cases since renal conservation of sodium is supposed to be controlled by the adrenal cortex.

Considerable evidence has accumulated to indicate that various zones of the adrenal cortex are concerned with the production of different cortical hormones. It has been assumed that the inner zone produces androgens, the mid-zone metabolism-controlling hormones and the outer zone electrolyte-regulating corticoids.[6,7] The outer zone is therefore of particular interest in the case of hypertensive patients treated with the rice diet.

Experimental studies have been made in animals in regard to the effect of sodium and potassium intake on the adrenal cortex.[8-10] Sodium deficiency or potassium excess resulted, in rats, in increased size of the zona glomerulosa whereas sodium excess or potassium deficiency was reflected in a decrease.

In view of these considerations it appeared worth while to study the morphologic state of the adrenal cortex, particularly the zona glomerulosa, in hypertensive patients who died while on the (salt-free) rice diet. These were compared with the adrenals of hypertensive patients who died while on a normal diet, with the adrenals of patients dying from wasting diseases not associated with hypertension and with the adrenals of patients dying suddenly without preceding illness.

MATERIAL

The adrenals studied include those of fifty-four hypertensive patients on the rice diet who died during the years 1943 to 1952. The patients were on the rice diet regimen for at least five weeks, averaging eight months. The diagnoses were: terminal stage of chronic glomerulonephritis in seventeen instances, of chronic pyelonephritis in ten instances; polycystic kidney disease in one case; dissecting aneurysm in one case; arteriolonephrosclerosis (essential hypertension), with various complications, in sixteen instances; malignant hypertension in nine instances.

These patients, representing all available autopsy material, are a selection insofar as most of them did not respond satisfactorily to the

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dietary treatment. The blood pressures in the last week prior to death averaged 185/111; the blood pressure average before starting the diet was 215/133. Kidney function, as indicated by PSP tests (phenolsulfonphthalein excretion), was severely impaired in the majority of the cases, total PSP excretion in two hours being below 10 per cent in twenty-three of the fifty-four patients; 10 to 24 per cent in fourteen; 25 to 49 per cent in ten; 50 per cent or above in only four (PSP value was not available in three patients). The serum electrolytes were deranged during the terminal ten days in thirty-five of the fifty-four patients, with hyponatremia of varying degree and, in some instances, hyperpotassemia. The frequency of serum electrolyte imbalance in this particular group of patients is another expression of the severe impairment of kidney function in the majority of them.[11]

Ten of the fifty-four patients died suddenly following cerebral hemorrhage, myocardial infarction or dissecting aneurysm. They had been on the rice diet for periods of five weeks to several years, averaging twenty-one months. These ten patients were considered also separately as a subgroup because of their relatively undisturbed metabolic status prior to death.

For comparison, we examined the adrenals of thirteen hypertensive patients who died while on a normal diet with normal salt intake. These patients were as severely hypertensive as the others; most of them died suddenly from cerebral hemorrhage or myocardial infarction.

In addition, the adrenals of fifteen malnourished patients with gastrointestinal cancer were examined for general comparison with the hypertensive groups, and for specific comparison with those of the fifty-four hypertensive patients who died after a terminal period of insufficient nutrition, as in the last stage of uremia.

The adrenal glands of twenty patients who died suddenly without preceding illness (accidents, etc.) were used as controls.

In order to correlate the observations on human adrenals with additional observations on rat adrenals, five groups of rats were studied: non-hypertensive and hypertensive rats on normal and salt-free (rice) diets, respectively, and hypertensive rats on a rice diet with supplementary sodium chloride. The hypertension was produced by renal encapsulation and subsequent contralateral nephrectomy. The average of the last systolic blood pressures in the hypertensive rats on a normal diet was 217 mm. Hg, in the hypertensive rats on a rice diet 150, in the hypertensive rats on a rice diet with supplementary sodium chloride 191. The food was offered ad libitum. The daily food intake was measured; there was fluctuation from day to day in the individual rat but the average consumption did not vary considerably among rats on the same type of food. Excluding the last days prior to death in the hypertensive animals (when it usually decreased), the daily intake averaged 13 gm. for the normal food (dog chow) and 36 gm. for the rice diet, representing 45 and 44 calories, respectively. The amount of supplementary sodium chloride in group 5 corresponded to that consumed in the normal food (100 mg. NaCl per day); the salt was given in solution in special 5 cc. containers which had to be emptied before tap water was permitted ad libitum.

All animals were of comparable age, about six months old at the time of death. At that time the body weight of the hypertensive animals was lower than that of the normal animals. However, the weight averages for the various groups of hypertensive rats were similar, as were the weight averages for the groups of normal rats, which indicates that the diet, whether salt-containing or salt-free, did not influence the weight of the animals. The normal rats were killed. The hypertensive rats died spontaneously and were chosen, out of many such animals, to match the age of the others; at the time of death rats on a normal diet had hypertension from 8 to 110 days, averaging 36 days; rats on the rice diet from 117 to 140 days, averaging 130 days; rats on the rice diet with supplementary sodium chloride from 8 to 119, averaging 64 days.

METHODS

Three methods of study were used: 1. Cross sections of the adrenal glands, fixed in Helly's fluid, blocked in paraffin and stained with hematoxylin and eosin, were examined. The thickness of the zona glomerulosa was measured in ten separate random areas with a Spencer 10× eyepiece micrometer which was calibrated against a Bausch and Lomb stage micrometer ruled to 0.01 mm. The average thickness of the glomerulosa was calculated. In some cases ten or twenty additional measurements were made; there was no significant deviation of the average based on twenty or thirty observations from the average based on ten measurements, though many adrenals showed great variability in thick-

ness and fat content from area to area. The observer who made the measurements did not have knowledge of the case history.

II. In the hematoxylin-eosin sections a subjective estimate of the fat content of the glomerulosa was made and each classified as minimal, little, moderate or abundant, corresponding to 1+, 2+, 3+ or 4+.

III. The lipids of the zona glomerulosa were studied histochemically by methods previously used[8,9,12-15] in four hypertensive patients on the rice diet and seven controls, in whom 10 per cent formalin-fixed adrenal tissue was available. Eight frozen sections cut at 15 μ were made in each case and treated as follows: (1) stained for fat with Sudan IV stain; (2) unstained section examined for birefringence in polarized light; (3) stained by Schultz method[8,13] and immediately examined for the blue-green color which develops in the presence of carbonyl groups; (4) stained by phenylhydrazine reaction[8,13] which gives a yellow color with plasmalogens; (5) stained by the Feulgen plasmal reaction[8,12,14,15] (positive reaction indicated by the red-purple color of the Schiff reaction); (6) extracted in acetone for thirty minutes and stained by Schultz method; (7) extracted in acetone and stained by the Feulgen plasmal reaction; (8) extracted in acetone and examined for birefringence. Any sudanophilic, acetone-soluble, birefringent, Schultz-positive, phenylhydrazine-positive, Schiff-positive droplets present within the cytoplasm were assumed to be ketosteroids since no other substances are known to give this combination of positive reactions.[12-14]

RESULTS

The normal width and fat content of the human zona glomerulosa were established in the twenty controls.

Table I shows that the width of the zona glomerulosa of hypertensive patients on a normal diet (group 3) is the same as that of the controls (group 1). The malnourished cancer patients (group 2) show a slight decrease in width. In the fifty-four hypertensive patients on a rice diet (group 4) the average width of the zona glomerulosa was considerably increased. In the ten of these who died suddenly without preceding metabolic disturbance (group 4A) the average width of the zona glomerulosa was increased but not to the same degree as in the group as a whole.

The combined weights of both adrenal glands were obtained from the autopsy protocols where they were listed routinely. There was no significant difference in the average weight of the adrenals in the various groups although a wider spread was noted in hypertensive patients.

TABLE I

WIDTH OF ZONA GLOMERULOSA IN HUMAN PATIENTS
(Averages with Standard Deviations and Ranges)

Group		Diet	No. of Pts.	Combined Wt. of both Adrenals (gm.)	Width of Zona Glomerulosa (in μ)
1	Controls (accidental, sudden death)	Normal	20	21 ± 4.5 (13–30)	136 ± 39 (93–234)
2	Patients with carcinoma of gastrointestinal tract	Normal, but insufficient intake	15	20 ± 4.2 (12–25)	104 ± 25 (56–139)
3	Hypertensive patients	Normal	13	24 ± 9.9* (10–40)	130 ± 21 (98–162)
4	Hypertensive patients	Salt-free (rice diet)	54	23 ± 9.9 (8–50)	181 ± 79 (83–425)
4A	Hypertensive patients (selected)	Salt-free (rice diet)	10	19 ± 5.6 (12–27)	168 ± 56 (114–264)

* With inclusion of 30 additional cases: 19 ± 6.8 (7–40)

Figures 1 to 8 give examples of the microscopic appearance of the zona glomerulosa in human patients. In comparing Figures 1 and 2 which are hematoxylin and eosin stains of the adrenals of a control patient on normal diet and a hypertensive patient on salt-free (rice) diet, respectively, the increased width of the zona glomerulosa in the latter case is apparent. Similarly, Figures 3 and 4 demonstrate on fat stains the difference in width of the zona glomerulosa of a control patient on a normal diet and a hypertensive patient on a salt-free diet. Figure 5 shows the narrow zona glomerulosa of a hypertensive patient on a normal diet. Figure 6 shows the narrow zona glomerulosa of a patient with cancer of the stomach who, like some of the hypertensive patients with uremia, had gone through a period of insufficient food intake prior to death. Figure 7 demonstrates the presence of phenylhydrazine-positive fat, and Figure 8 shows a nodular type of hyperplasia of the zona glomerulosa, both in adrenals from hypertensive patients on the rice diet.

Table II gives an analysis of the hypertensive

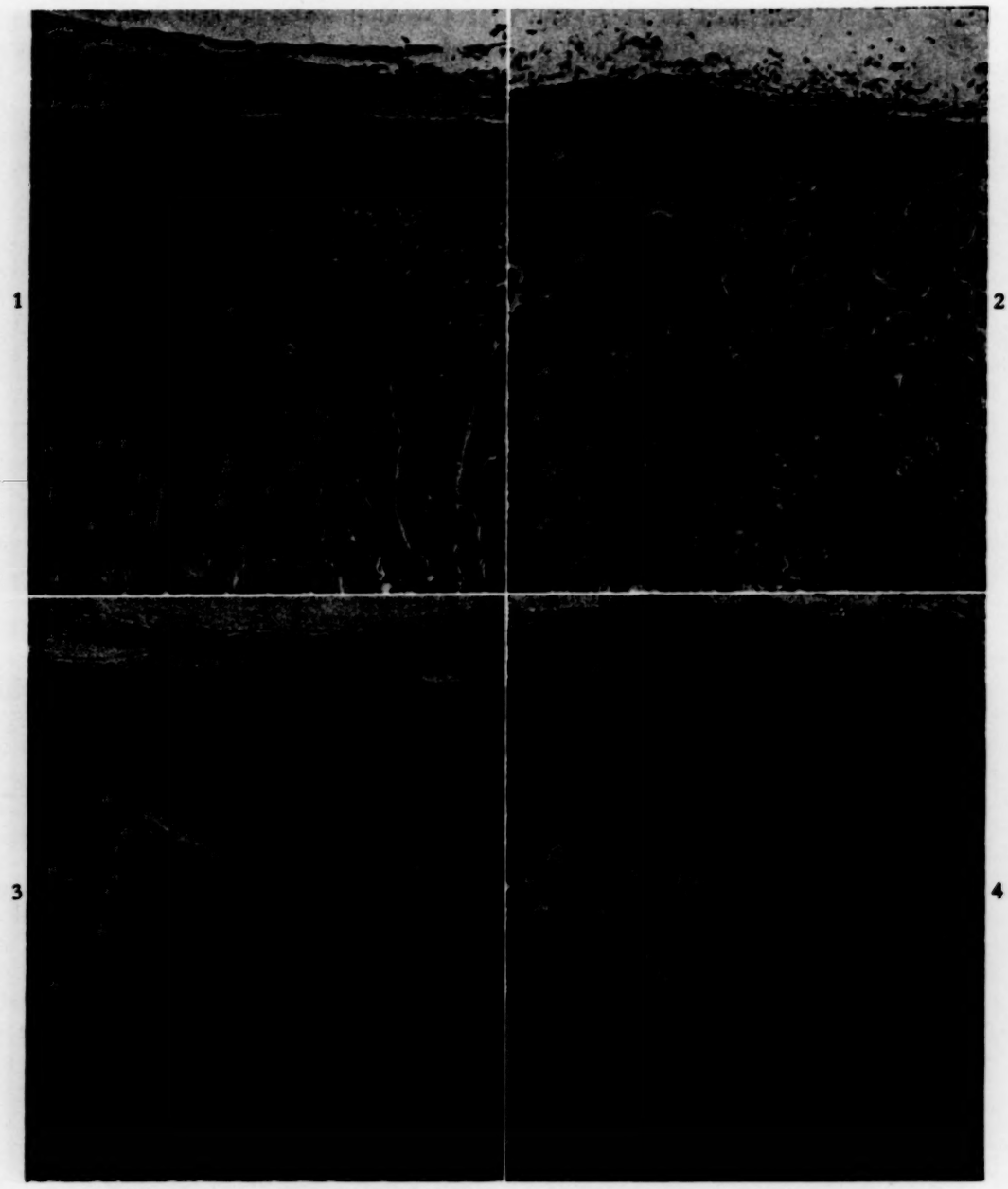

FIG. 1. Control human adrenal, showing thin zona glomerulosa with abundant fat, clearly demarcated from zona fasciculata which contains less fat; hematoxylin and eosin, × 123.

FIG. 2. Adrenal from hypertensive patient on salt-free (rice) diet, showing hyperplastic zona glomerulosa with little cytoplasmic fat. The zona fasciculata contains abundant fat; hematoxylin and eosin, × 123.

FIG. 3. Control human adrenal, stained with Sudan IV for fat, showing abundant cystoplasmic fat in zona glomerulosa, with less fat in zona fasciculata. Frozen section; × 140.

FIG. 4. Adrenal from hypertensive patient on the rice diet, Sudan IV fat stain, showing hyperplastic zona glomerulosa with moderate cytoplasmic fat. In this case the zona fasciculata contains abundant fat. Frozen section; × 149.

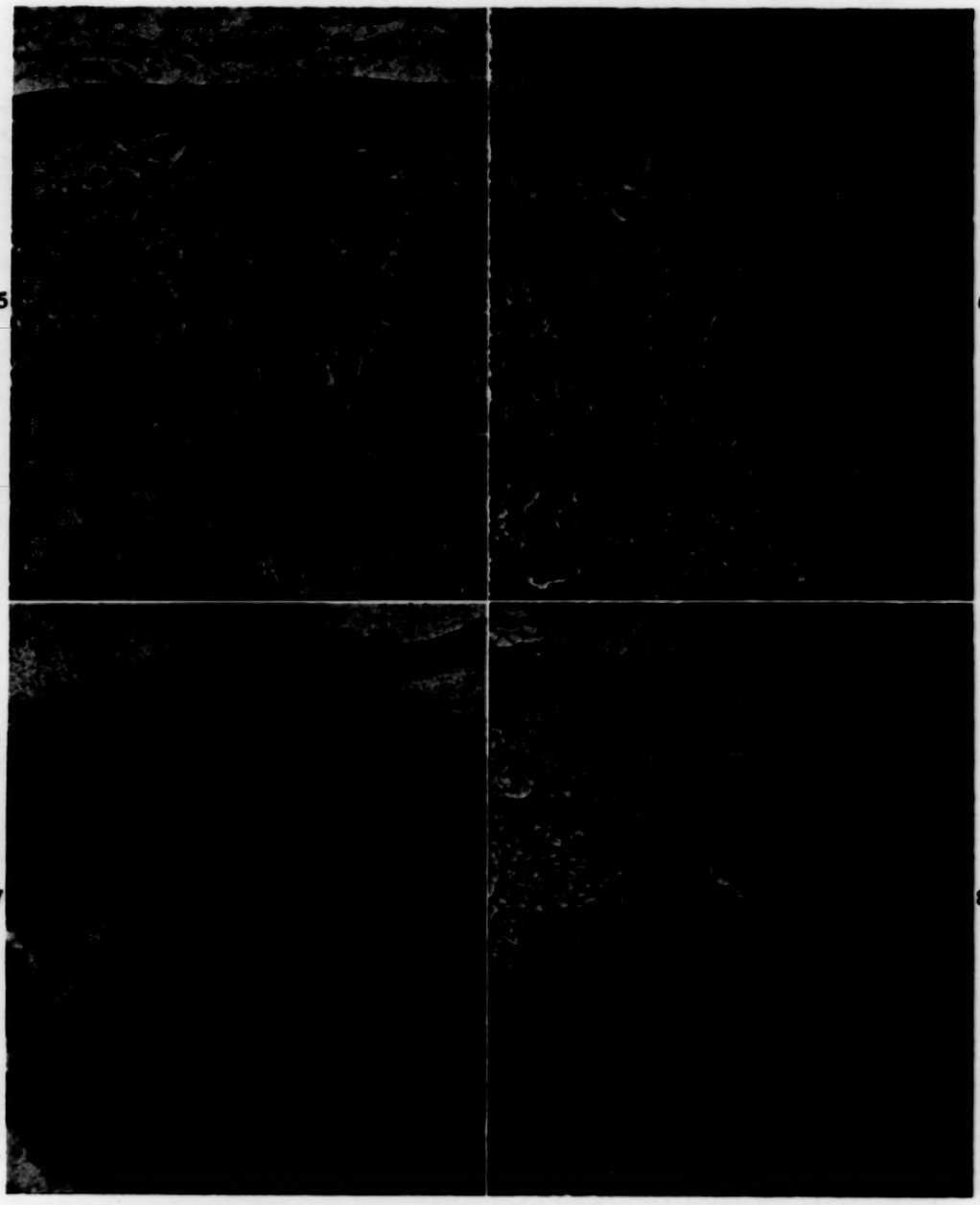

FIG. 5. Adrenal from hypertensive patient on normal diet without salt restriction, showing thin zona glomerulosa with minimal cytoplasmic fat; hematoxylin and eosin, × 123.

FIG. 6. Adrenal from malnourished cancer patient, showing thin zona glomerulosa with depleted cytoplasmic lipids; hematoxylin and eosin, × 123.

FIG. 7. Adrenal from hypertensive patient on the rice diet, phenylhydrazine stain, showing moderate phenylhydrazine-positive fat in zona glomerulosa (upper half of picture) with slightly less in zona fasciculata. Frozen section; × 149.

FIG. 8. Adrenal from hypertensive patient on the rice diet, showing nodular area of hyperplasia of zona glomerulosa with marked variation in the fat content of the zona glomerulosa. The zona fasciculata contains a uniformly moderate amount of fat. Note the hyalinized arteriole; hematoxylin and eosin, × 123.

patients on the rice diet (groups 4 and 4A of Table I) in regard to the relation of the width of the zona glomerulosa to its normal range. It is seen that in the majority (70 per cent) of the fifty-four patients, the width of the zona glomerulosa was within the normal range. In 6 per cent it was below normal; in 24 per cent it was above normal. Of the three cases below normal, all fall within two standard deviations from the average. In contrast, all of the thirteen cases above the normal range lie outside two standard deviations from the average. The ten selected hypertensive patients (group 4A) show a distribution similar to the total group.

TABLE II

WIDTH OF ZONA GLOMERULOSA IN HYPERTENSIVE PATIENTS ON RICE DIET

(Averages with Standard Deviations and Ranges, in μ)

	Width below Normal Range			Width within Normal Range			Width above Normal Range		
	No. of Pts.	Combined wt. of both Adrenals (gm.)	Width of Zona Glomerulosa	No. of Pts.	Combined wt. of both Adrenals (gm.)	Width of Zona Glomerulosa	No. of Pts.	Combined wt. of both Adrenals (gm.)	Width of Zona Glomerulosa
Controls (20)	.....	.....	.....	20	21 ± 4.5 (13–30)	136 ± 39 (93–234)	.....	.....	.....
Hypertensive patients on rice diet (54)	3 (=6 %)	22 ± 2.6 (20–25)	84 ± 2 (83–86)	38 (=70 %)	23 ± 11.0 (8–50)	149 ± 34 (96–226)	13 (=24 %)	24 ± 7.1 (18–40)	296 ± 62 (235–425)
Selected hypertensive patients on rice diet (10)	.....	.....	.....	8 (=80 %)	19 ± 5.6 (12–27)	144 ± 28 (114–179)	2 (=20 %)	Not Available	263 ± 2 (261–264)

TABLE III

WIDTH OF ZONA GLOMERULOSA IN RATS

(Averages with Standard Deviations and Ranges)

Group		Diet	No. of Animals	Width of Zona Glomerulosa (in μ)
1	Normal rats	Normal (dog chow)	20	41 ± 7 (32–51)
2	Hypertensive rats	Normal (dog chow)	12	48 ± 11 (34–61)
3	Normal rats	Salt-free (rice diet)	9	107 ± 35 (69–160)
4	Hypertensive rats	Salt-free (rice diet)	14	122 ± 47 (61–206)
5	Hypertensive rats	Rice diet +NaCl	14	47 ± 9 (32–61)

The results of the measurements of the width of the zona glomerulosa in rats are combined in Table III. It is seen that hypertensive rats on a normal diet (group 2) have a small increase in the width of the zona glomerulosa, an observation which will be subject to further study. Hypertensive rats on a salt-free (rice) diet have a very marked increase in size of the zona glomerulosa (group 4). Similarly, normal rats on a salt-free diet (group 3) show a marked increase in the width of the zona glomerulosa. When the rice diet was supplemented with sodium chloride (group 5) the width of the zona glomerulosa was like that of rats on a normal diet.

Figures 9 to 12 give examples of the microscopic appearance of the zona glomerulosa in rats. All four pictures apply the same staining technic and the same magnification. Figures 9 and 10 are from normal rats on the normal diet and salt-free (rice) diet, respectively. The

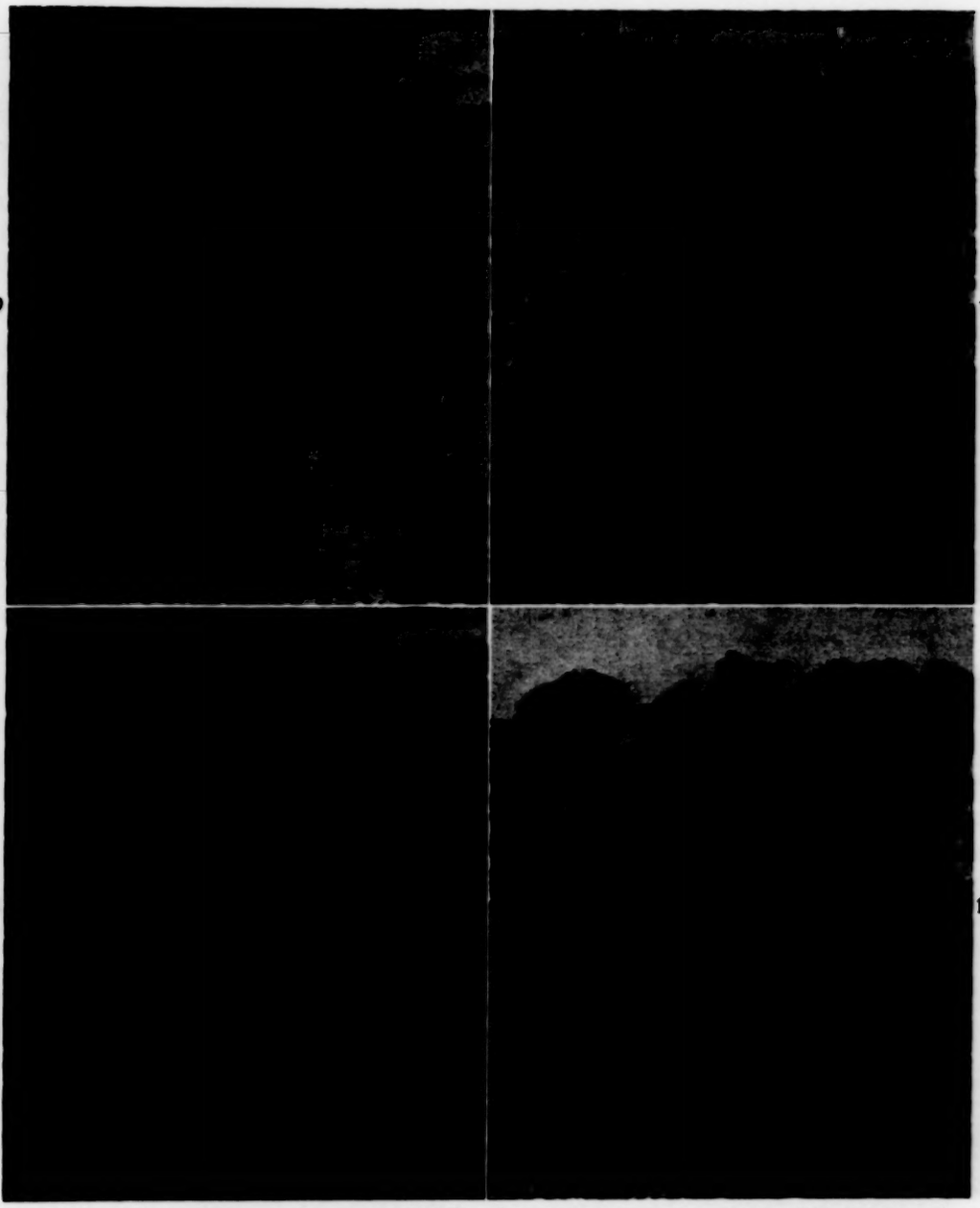

FIG. 9. Adrenal from normal rat on normal diet. Note the thin zona glomerulosa (upper one-fifth of photograph) with abundant cytoplasmic fat; hematoxylin and eosin, × 245.

FIG. 10. Adrenal from normal rat on salt-free rice diet. Note the greatly enlarged zona glomerulosa (upper two-thirds of photograph) which in this case contains abundant cytoplasmic fat. The zona fasciculata contains little fat; hematoxylin and eosin, × 245.

FIG. 11. Adrenal from hypertensive rat on normal diet containing normal supply of salt. Note the thin zona glomerulosa (upper one-fifth of photograph) with little cytoplasmic fat; hematoxylin and eosin, × 245.

FIG. 12. Adrenal from hypertensive rat on salt-free rice diet. Note the greatly enlarged zona glomerulosa (upper two-thirds of photograph) containing abundant cytoplasmic fat; hematoxylin and eosin, × 245.

increased size of the zona glomerulosa in Figure 10 is apparent. Figures 11 and 12 are from hypertensive rats on the normal and salt-free diet, respectively, Figure 12 showing hyperplasia of the zona glomerulosa in the animal on the salt-free diet.

TABLE IV
ESTIMATED FAT CONTENT* OF ZONA GLOMERULOSA IN HUMAN PATIENTS

Group		Width below Normal Range		Width within Normal Range		Width above Normal Range	
		No. of Pts.	Av. Fat Content	No. of Pts.	Av. Fat Content	No. of Pts.	Av. Fat Content
1	Controls (20)	..	.....	20	2.8 +	..	.....
2	Patients with carcinoma of gastrointestinal tract (15)	6	1.8 +	9	2.1 +	..	.....
3	Hypertensive patients on normal diet (13)	..	.....	13	2.3 +	..	.....
4	Hypertensive patients on rice diet (54)	3	3.2 +	38	2.8 +	13	2.0 +
4A	Selected hypertensive patients on rice diet (10)	..	.....	8	2.8 +	2	1.5 +

* Expressed as 1+, 2+, 3+, 4+, corresponding to minimal, little, moderate, abundant.

Statistical analysis of the data contained in Table I indicates that: the differences in the averages of the adrenal weights are not significant for any group (P being >0.3 in all instances); in regard to the width of the zona glomerulosa, the difference of the means for groups 4 and 1 is significant (P between 0.02 and 0.01), there is no significant difference with regard to groups 3 and 1 ($P > 0.5$), the difference of the means for groups 2 and 1 is significant ($P < 0.01$), and the difference of the means for groups 4A and 1 is of borderline significance (P between 0.05 and 0.06). The enlargement in 24 per cent of the cases of group 4 of Table I, as represented in Table II, is statistically highly significant ($P < 0.01$). Statistical analysis of the data contained in Table III indicates that: the differences of the means for groups 2 and 5, respectively, compared with group 1, are significant (P between 0.05 and 0.02); the differences of the means for groups 3 and 4, respectively, compared with group 1 are highly significant ($P < 0.01$ in both cases); whereas the difference of the means for groups 3 and 4 is not significant (P about 0 .4).

The estimated mean fat content of human adrenals, applying the 1 to 4+ scale, was 2.8+ in the controls. (Table IV.) It is seen in the other groups that where the width of the zona glomerulosa was within the normal range, the fat content was approximately the same, except for the malnourished cancer patients in whom it was decreased. In group 4 it seems that as the width of the zona glomerulosa increased the fat content decreased. In rats the fat content was extremely variable within individual groups.

Of the four adrenals from hypertensive patients on the rice diet in which studies could be made with special histochemical methods, all were within the normal range of zona glomerulosa width, averaging 122 μ. The fat content of these cells was slightly higher than in seven controls similarly examined. The fat which was present gave the same reactions in hypertensive patients as in controls. It was sudanophilic, acetone-soluble, birefringent, Schultz-positive, phenylhydrazine-positive and Schiff-positive. It is therefore assumed to represent ketosteroids.

COMMENTS

Deane, Shaw and Greep[8,9] and Bacchus[10] demonstrated that in rats a reduced sodium intake or excessive potassium intake resulted in a conspicuous increase in the width of the zona glomerulosa, with reduction in the cytoplasmic lipid droplets. This occurred in both hypophysectomized and normal rats. They interpreted this to mean increased secretion of desoxycorticosteroids by the cells of the zona glomerulosa secondary to a lowered sodium: potassium ratio.

Our observations on rats given a sodium-free (rice) diet confirm their findings, as evident in groups 1 and 3 of Table III. We extended the study to include hypertensive rats on the normal and salt-free diets, and found the same results as in non-hypertensive rats (groups 2 and 4 of Table III). When the rice diet was supplemented with sodium chloride, the width of the zona glomerulosa was like that on a normal, mixed diet. It is apparent by comparing the five groups of Table III that reduced salt intake is the decisive factor in producing the increased size of the zona glomerulosa. Some enlargement was found

to be caused by hypertension alone (groups 1, 2 and 5 of Table III). This is in agreement with the observations of Deane and Masson.[16]

All of the fifty-four human hypertensive cases listed as group 4 in Table I were on a diet of lowered sodium:potassium ratio. In addition, the majority of them were in renal failure and had serum electrolyte disturbances with a lowered sodium:potassium ratio in the serum. The morphologic studies showed a significant increase in the width of the zona glomerulosa in 24 per cent (Table II) when compared with the adrenals from cases of sudden death without antecedent illness (group 1, Table I) or with hypertensive patients not on a salt-free diet (group 3, Table I).

The malnourished cancer patients (group 2, Table I) showed a decrease in size of the zona glomerulosa when compared with normal and hypertensive patients including those hypertensive patients in whom the terminal uremic phase had resulted in reduced food intake.

The increase in width of the zona glomerulosa observed in both human patients and rats when on a sodium-free diet is a morphologic fact which may be subject to different interpretations. If interpreted as Deane, Shaw and Greep interpreted their findings in the rat, it would indicate an increase in the activity of the zona glomerulosa due to the lowered sodium:potassium ratio of the diet.

The observations on the fat content of the glomerulosa cells indicated that when the width was increased, the fat was decreased. This could be interpreted as an indication of increased hormone production without storage. The special histochemical technics identified the cytoplasmic fat as ketosteroid in type.

It is apparent that these groups of patients do not allow any conclusions in regard to the participation of adrenal cortical activity in the primary genesis of hypertension.

With regard to the influence of the rice diet generally on the adrenal cortex, apart from the factor of salt restriction, no definite conclusions can be drawn since the cases which could be examined belonged mainly to those which failed to respond to the dietary treatment. In addition, the present series of fifty-four patients on the rice diet is "atypical" insofar as 65 per cent were in serum electrolyte derangement whereas in a "typical" group of hypertensive patients on the rice diet serum electrolyte imbalance would be found in only 5 per cent.[5] Nevertheless, adrenal cortical atrophy as an indication of reduced cortical activity was not observed in any of the fifty-four patients.

SUMMARY

1. The zona glomerulosa of the adrenals of fifty-four hypertensive patients who died while on the salt-free rice diet was compared with that of twenty patients who died suddenly without preceding illness, with thirteen hypertensive patients on a normal diet, and with fifteen malnourished cancer patients.

2. Due to advanced renal insufficiency, serum electrolyte disturbances including hyponatremia occurred terminally in thirty-five of the fifty-four patients on the rice diet.

3. The width of the zona glomerulosa of the patients on the rice diet was found to be increased significantly, by statistical methods, in 24 per cent of the cases. It was within the normal range in 70 per cent and insignificantly below the normal range in 6 per cent.

4. Hypertensive rats on a salt-free diet compared to hypertensive rats on diets with normal salt content showed a marked increase in width of the zona glomerulosa. Similarly, normal rats on a salt-free diet compared to normal rats on a normal diet showed a marked increase in width of the zona glomerulosa. The latter observation is in agreement with the observations of several other authors.

5. The cytoplasmic fat content was decreased in the human adrenals when the width of the zona glomerulosa was greater than normal, and was the same as in the controls when the width was in the normal range. Special histochemical staining technics identified the cytoplasmic fat as ketosteroid in type.

6. No conclusions can be drawn regarding the role of the adrenal cortex in the genesis of hypertension.

7. In regard to the influence of the rice diet on the adrenal cortex, definite cortical atrophy, such as would indicate reduced cortical activity, was not observed in a single instance.

8. The increased width and decreased fat content of the zona glomerulosa are interpreted as evidence of increased hormone production without storage. It is suggested that this may be due to the decreased sodium:potassium ratio which stimulates the production of electrolyte-regulating corticoids.

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Variability of the Rate of Coagulation of Whole Blood*

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WITH the advent of technics for measuring quantitatively the various components concerned in blood clotting, the use of fresh whole blood clotting time as a measure of the coagulability of the blood has fallen into disrepute. Quick[1] has suggested that it be discarded and Wright[2] has stated that it "is one of the most complex and unreliable tests." In spite of the case against this test we believe that it has value because (1) it is usually this clinical test which leads to employment of the tests for specific components, (2) there are still defects in coagulation for which there are no specific tests and (3) every newly discovered accelerator or inhibitor must eventually be related to blood clotting. The answer to the problem lies in determination of the variables in, not avoidance of the test. Every author of a test for a specific component of blood coagulation describes in detail the technic, the quantity and composition of components, ionic strength, dilution and any other factors concerned. This has not been done for whole blood coagulation.

For several years we have been interested in the effects of food on blood clotting. It has been shown that oral ingestion of fat accelerates blood clotting[3] and that this reaction is altered by feeding sugar[4] or by disease.[5] In the course of these studies of over 1,000 patients we have noted several factors which affect the rate of coagulation. In addition we have recently studied the problem of the technic of blood coagulation because Wright[2–6] has reported that his laboratory has difficulty in finding variation in clotting time with food. This report is concerned with some of the variables and the description of a standard technic that gives reproducible results in the individual.

METHOD

Various technics were employed in obtaining samples of venous blood. With each experiment the variation from the standard technic will be mentioned. A 5 ml. or 10 ml. glass syringe with a glass tip was used for collecting blood. The Luer-lok tip does not allow easy transfer of blood to the clotting tube without force. An 18 or 20 gauge needle with a very sharp point was used. Needles of less than 20 gauge slowed collection of the sample. Prior to the venipuncture 1 to 2 ml. of sterile 0.85 per cent sodium chloride solution was drawn through the needle into the syringe and allowed to wet the entire barrel of the syringe. All of the saline was then ejected prior to the venipuncture. This maneuver facilitates the movement of the plunger in the syringe during the actual collection of blood. The tubes used to measure the coagulation time were thin-walled soda-lime glass 60 mm. high and 15 mm. wide with a rounded bottom.

In the process of venipuncture the vein to be used was located and the tourniquet was placed on the arm immediately before venipuncture. This prevented venous stasis of more than forty-five seconds. The venipuncture was made with one stroke through the skin to the lumen of the vein. The slightest amount of probing with the needle in the subcutaneous tissues altered the results. In repeated venipunctures the hole of a previous venipuncture was never utilized. Three ml. of blood were collected rapidly with gentle suction and without foaming of the blood. One ml. of blood was first placed in tube two of the clotting tubes and one ml. was placed in tube one. Tube one was the tube which was tilted first. The last ml. of blood in the syringe was discarded. The procedure of drawing an extra ml. avoided the necessity of forcibly ejecting the blood put into tube one. The time from the first entry of blood into the syringe until the blood was placed in both clotting tubes did not exceed thirty seconds.

Measurement of the clotting time was performed by a two-tube technic with the glass

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tubes previously described. These tubes were lined with either silicone or collodion as mentioned in each experiment. The tubes were stoppered with corks after the blood was introduced and were placed in a constant temperature water bath at 38° ± 1°C. Tube one was tilted every thirty seconds until its contents had clotted; then tube two was tilted every thirty seconds until a clot formed. This latter reading was taken as the clotting time. The formation of a solid clot which permitted complete inversion of the tube without spillage of its contents indicated the end point. This end point could not be used with siliconized glassware. The timing of the clotting process was begun immediately upon placing the first blood in tube two.

TABLE 1
COMPARISON OF THE WHOLE BLOOD CLOTTING TIMES BEFORE AND AFTER THE ORAL ADMINISTRATION OF CREAM USING A COLLODION TECHNIC AND A COMPLETE SILICONE TECHNIC

Time after Cream	Clotting Time (sec.)		Change (%)	
	Collodion	Silicone	Collodion	Silicone
Fasting	1,770	2,340	....	....
Fed 60 ml. of Cream				
One-half hr.	1,320	1,650	25.3	29.4
One hr.	1,170	1,600	33.8	31.4
Two hr.	1,410	1,770	20.3	24.3
Three hr.	1,440	2,190	18.6	16.4

Flexible collodion (U. S. P.) was used to coat the tubes when collodion tubes were used. Silicone-lined glassware was prepared with General Electric Dri-film No. 9987 according to the method described by Jaques[7] using petroleum ether as a diluent. Whenever clotting times were measured in silicone-lined tubes, the blood was collected with a silicone-lined syringe and needle. Armour's bovine fibrinogen was used whenever indicated.

RESULTS

Effect of Surface. It is generally agreed that a plain glass surface accelerates the clotting process to such an extent that slight defects in coagulation may not be detectable with this technic. Efforts have been made to obtain a better surface. These range from paraffin coating through lustroid tubes and collodion-lined tubes to the recent introduction of silicone. The last two surfaces have received the widest acceptance. Studies were made to determine the relative value of these two surfaces.

A comparison of clotting times of fresh whole blood in collodion-lined tubes with those obtained in silicone-lined tubes in seventy-five subjects revealed that in 20 per cent of the individuals there is no appreciable difference in clotting time between these two surfaces. In this 20 per cent the clot formed in silicone is fairly firm and the end point is easily determined. In 80 per cent of the individuals the silicone technic resulted in a clotting time ten to twenty minutes longer than when the collodion technic was employed. The end point of clotting in silicone in this group was entirely different than the clot formed in collodion because in the silicone tube the interval from the very beginning to the end of clot formation was a long time. During this time the blood which clotted first was undergoing syneresis. Thus at no time did the whole volume form a solid mass because serum was being extruded from the portion which had clotted first at the time the last portion was clotting. As an end point one had to take the time when the greatest amount of clotting was present. The end point therefore was one of interpretation. Barker[8] reports that this presents no difficulty when blood is clotted at 37°C. Brinkhous[9] reported the same difficulty encountered in the present experiment.

When the reading of the end point in silicone was mastered, the changes in clotting time after feeding 60 ml. of cream in both a silicone-lined and collodion-lined tube were compared. These studies were performed in twenty-five subjects with essentially the same results. A typical experiment is shown in Table 1. Although silicone gave a longer clotting time than collodion, the patterns of response were similar. The evanescence of the end point in silicone-lined tubes when doing clotting times of whole blood makes this technic subject to considerable error. The collodion technic gives a sufficiently long clotting time in which to detect small fluctuations and in addition gives an easily identified end point.

Effect of Changing Syringes. It is said that one of the causes of accelerated clotting times is the acquisition of a small amount of tissue thromboplastin during the venipuncture. This factor can be eliminated by doing the venipuncture with one syringe and collecting a few ml. of blood

in it; then a new syringe is switched onto the needle which has remained *in situ* and the blood obtained in the second syringe is used for clotting. The advantage of this procedure was investigated in connection with the problem of whether or not re-using a syringe affects the

TABLE II
COMPARISON OF THE WHOLE BLOOD CLOTTING TIMES BEFORE AND AFTER THE ORAL ADMINISTRATION OF CREAM USING THE "SWITCHED-SYRINGE" TECHNIC

Time after Cream	Clotting Time (sec.)			Change (sec.)		
	Syringe I	Syringe II	Syringe III	Syringe I	Syringe II	Syringe III
Fasting...	1,020	1,140	1,350	....	....	....
Fed 60 ml. of Cream						
One-half hr.....	1,110	1,230	1,260*	+90	+90	....
One hr....	1,080	1,230	1,410	+60	+90	+60
Two hr...	960	1,050	1,290	−60	−90	−60

* Poor sample.

results. For the purpose of this study we tried three syringes and one venipuncture at each period. Syringe I was used for the initial venipuncture. After washing in running water and rinsing in physiologic saline this syringe was used for all venipunctures. Syringe II was adjusted to the needle after syringe I was removed. After adequate washing this syringe was used at each period of testing. Syringe III was actually several syringes because in this instance a different sterile syringe was used at each period. The clotting times in collodion-lined tubes are presented in Table II.

This particular experiment was chosen because it adequately answers the question of whether repeated use of the same syringe is justified. Table II depicts the findings in the case of a patient whose clotting time was not altered by oral ingestion of fat. If the syringes could not be washed adequately for re-use, one would have expected an accelerated clotting time due to the accumulation of blood products. This did not occur. The changes with syringe I and II, the "re-used" syringes, gave the same results as syringe III, namely, a new syringe for each observation. It will be noted that although the control clotting time is different in each instance, the absolute change in seconds is within a range of ± thirty seconds. This is the interval at which the tubes are observed.

Table III presents the results of experiments on ten subjects who were studied for three hours after being fed 60 ml. of cream. Zero time represents the control before the ingestion of fat. The "re-used" syringe was employed for all venipunctures and the clotting times of blood obtained in this syringe were recorded. A separate sterile syringe was switched on to the needle *in situ* and the clotting times of the blood obtained in these syringes were recorded. All syringes were plain glass except in the last four experiments. In these a complete silicone technic was used with both syringes. The same pattern of response was obtained with "re-used" syringes and separate sterile syringes and was independent of surface of the syringe. A silicone technic shifts the response quantitatively but not qualitatively.

TABLE III
COMPARISON OF THE WHOLE BLOOD CLOTTING TIMES BEFORE AND AFTER THE ORAL ADMINISTRATION OF CREAM USING "RE-USED" AND STERILE SYRINGES

	"Re-used" Syringes					Sterile Syringes				
Hours	0	½	1	2	3	0	½	1	2	3
Subject:										
A. G.	990	870	720	930	960	1,080	900	800	1,080	1,080
H. C.	1,200	750	960	1,020	1,110	1,350	990	1,100	1,160	1,200
J. R.	1,650	1,800	2,070	2,160	2,070	1,890	2,130	2,280	2,250	2,100
V. McC.	1,440	1,230	930	1,170	1,390	1,620	1,350	1,110	1,320	1,350
B. G.	1,320	1,030	840	990	1,200	1,470	1,170	840	1,020	....
B. M.	1,230	960	810	960	1,050	1,260	1,110	840	900	1,170
J. M.*	2,490	2,250	1,800	2,220	....	2,730	2,430	2,070	2,220	....
I. R.*	3,540	2,900	1,950	3,000	....	3,660	2,880	1,920	3,120	....
J. R.*	3,460	3,140	1,980	2,700	3,060	3,600	3,090	2,010	3,150	3,270
F. S.*	3,120	2,520	1,920	2,670	3,180	3,270	2,460	1,770	2,700	3,000

* Studies performed with complete silicone technic.

Does Switching Syringes Substitute for Good Technic? Another fact is apparent from Table II. Switching syringes does give a longer clotting time but switching the second time gives an even longer clotting time. The pattern of response with each of the syringes is the same. This brings up the question of whether multiple switchings would give even longer times and, if so, when does one stop switching? This problem was investigated by using six syringes, one for the venipuncture and five switches. At the same time the problem of whether the switching of syringes would compensate for a break in technic or for the inexperience of the technician was investigated. This was accomplished by (1) drawing the sample in syringe III slowly, (2) by using an inexperienced technician with syringe V and

(3) by drawing the blood in a manner which produced foam in syringe VI. The clotting times in collodion-lined tubes are presented in Table IV.

The third switch (syringe IV) produces a longer clotting time than the initial venipuncture or the initial switch. As shown in Table II the prolonged clotting time obtained by switching the syringes does not alter the response to orally ingested fat; it merely shifts the base line. These studies also show that the switched syringe technic does not substitute for experience and good technic.

TABLE IV

STUDY OF THE "SWITCHED-SYRINGE" TECHNIC EMPLOYING VARIOUS MODIFICATIONS IN FILLING EACH SYRINGE

	Clotting Time (sec.)			
Subject.....	1	2	3	4
Syringe I.....	1,140	1,170	1,290	1,110
Syringe II.....	1,200	1,280	1,380	1,140
Syringe III....	885	1,000	990	860
Syringe IV.....	1,310	1,360	1,590	1,380
Syringe V.....	930	1,050	.....	.....
Syringe VI.....	635	990	.....	1,130

Thrombin Accumulation in "Re-used" Syringes. It has been shown[6] that a fibrinogen solution will clot in syringes which have been "re-used." This question was investigated using thirteen syringes. Syringe I was used for the initial venipuncture and after washing was used for five successive venipunctures. After the first venipuncture twelve syringes were successively interchanged and two of these were saved. After the second venipuncture ten syringes were successively interchanged and two of them were saved. This procedure was followed in the remaining four venipunctures. There were then two syringes which had been used each of the following times: once, twice, three, four, five and six times. Three ml. of blood had been collected in each syringe. Two of the three ml. of blood from all syringes were placed in one test tube containing enough sodium citrate solution for 50 ml. of blood. This blood was then centrifuged at 1,400 r.p.m. for thirty minutes and the plasma used to determine whether it would clot if left in the syringes which had been "re-used." Four ml. of plasma were drawn into one syringe from the pair used from one to six times. The other syringe of the pair used from one to six times was filled with a 1 per cent solution of Armour's bovine fibrinogen in 0.85 per cent sodium chloride solution. One of the four ml. of solution (plasma or fibrinogen solution) from each syringe was placed in a test tube. The substance in both the tube and syringe was observed for the first trace of fibrin threads. The time of appearance is shown in Table V.

TABLE V

TIME IN MINUTES OF THE APPEARANCE OF THE FIRST FIBRIN THREADS IN A FIBRINOGEN SOLUTION AND IN PLASMA IN "RE-USED" GLASS SYRINGES AND IN SAMPLES TRANSFERRED TO COLLODION-LINED TEST TUBES

No. of Times Syringes Used	Fibrinogen Solution		Citrated Plasma	
	Syringe	Test Tube	Syringe	Test Tube
1	12	>180	>1,500	>1,500
2	13	81	>1,500	>1,500
3	15	37	>1,500	>1,500
4	15	37	>1,500	>1,500
5	>180	>180	>1,500	>1,500
6	>180	>180	>1,500	>1,500

If thrombin accumulates on "re-used" syringes, it is of no consequence in the conversion of plasma fibrinogen to fibrin. The fact that the plasma was citrated cannot explain the fact that a clot did not form because citrate interferes with the first stage and not the thrombin-fibrinogen reaction. In addition, Armour's fibrinogen did clot and this contains 50 per cent sodium citrate. The subject's plasma was capable of clotting because 1 ml. of blood from the first switched syringe in the first venipuncture had a clotting time of 1,230 seconds and 1 ml. of blood from the first switched syringe on the sixth venipuncture had a clotting time of 1,290 seconds. In addition, the subject's plasma could be clotted by thrombin because the addition of 0.01 ml. of thrombin solution (100 units/ml.) to 1 ml. of plasma resulted in the formation of a clot in fifteen seconds. The difference between the fibrinogen solution and plasma leads one to conclude that "pure" fibrinogen does not react the same as fibrinogen in plasma or, at least, bovine fibrinogen does not react the same as human fibrinogen. One must be careful in

using "pure" factors. They may be pure chemically but unrelated physiologically to the natural substance and one might draw conclusions about blood coagulation which are totally unrelated to the phenomenon.

Effect of Menstrual Cycle. The question of whether there are definite cyclic variations in clotting time coincident with the menstrual cycle has not been studied by us in sufficient detail but the response to the oral ingestion of fat is altered depending on the phase of the cycle in which the study is made.[10] One may obtain an accelerated clotting time or no effect after feeding cream to the same individual depending on the phase of the menstrual cycle. These findings are correlated with a difference in the partition of plasma lipids after feeding the cream. When the response to cream is an accelerated clotting time, there is a relatively greater increase in phospholipids over neutral fat postprandially. When there is no response to cream, the increase in plasma is primarily in the neutral fat fraction.[10]

Effect of Stress. Since the work of Vosburgh and of Richards[11] it has been known that epinephrine *in vivo* accelerates the clotting of blood. This has been ascribed[12] to an increased release of prothrombin but recent work[13] has shown that at least part of the effect can be a direct clot-accelerating effect of epinephrine because both epinephrine and nor-epinephrine *in vitro* accelerate clotting. Cognizance of the effect of endogenous epinephrine is the reason for insisting that the subject be calm, comfortable and not subjected to undue discomfort from the tourniquet or venipuncture. It is usually not realized that minor forms of stress which occur also affect clotting time. A typical result was obtained in a trained laboratory person who had a coagulation time of 1,170 seconds in the basal state. After dressing and taking the street car to work, a clotting time was measured after ten minutes' rest and found to be 810 seconds. After one hour's rest in a chair the clotting time was 1,110 seconds. All clotting times were measured in the fasting state. Other factors of environment may affect clotting time. This is exemplified by a typical experiment on another trained laboratory person accustomed to venipunctures. His normal clotting time determined on many occasions ranged between 1,020 and 1,320. After exposure to a temperature of 30°F. on coming to work his clotting time was 540 seconds and gradually returned to 980 seconds after ninety minutes. It is difficult to prove that the effect was due to cold but these factors should be considered in studies on blood coagulation, particularly on ambulatory patients. For reproducible results the subject must be under similar conditions for successive studies. The basal state is the most nearly reproducible state.

Effects of Food. In addition to environmental stresses, the clotting time may be affected by food. Previous reports have shown that the feeding of fat in the form of cream, refined corn oil or olive oil will accelerate blood coagulation.[3–14] This is associated with changes in plasma lipids.[10] The clot-accelerating effect of orally ingested fat may be mitigated by the simultaneous feeding of sucrose.[4] Not all fats increase coagulability. In Table VI butter, which is similar to cream in type of fat, is compared with oleomargarine, which contains more saturated fats. Each food was compared in the same patient on alternate days with an interval of one day between studies. In addition, one study is reported comparing refined corn oil with hydrogenated fat (Crisco). The difference between the effect of oleomargarine and butter is statistically significant, exceeding a value of 0.01 in each period except the third hour. Apparently the more saturated the fat, the less effect it has on blood coagulation.

Reproducibility of Results. Whole blood clotting times performed in the same manner as described in the section on methods, in which a glass syringe is used to collect the blood and the clotting time is measured in collodion-lined tubes, are reproducible in the same individual under identical circumstances. In a group of seventy patients in whom the rate of whole blood coagulation was measured on two days with only one day intervening between the test, the mean clotting times were 1022.1 ± 154 seconds and 1021.7 ± 176 seconds. This excellent agreement was not confined to the means. In considering the individual patients, the difference between clotting times on the two different days usually did not exceed 180 seconds. If the difference exceeds 180 seconds, it is usually due to the fact that the clotting time on the first day was short and could be ascribed to the anxiety of the venipuncture. If the clotting time is repeated a third time, the second and third clotting times usually agree within 180 seconds. In our studies all patients have been hospital patients who were convalescing from their

illnesses and who, by that time, were quite accustomed to venipunctures. In over 1,000 patients examined the average range according to this technic was 900 to 1,200 seconds.

The agreement in clotting times is not confined to the control period but also occur after merely an attempt to standardize the speed of the chemical reaction called blood coagulation and to facilitate comparison of studies made in different patients and in the same patient at different times.

Another factor which may be varied is the

TABLE VI

EFFECTS OF THE ORAL INGESTION OF SATURATED AND UNSATURATED FATS ON BLOOD COAGULATION

Food	No. of Subjects	Fasting Venous Clotting Time (sec.)	Percentage Change in Clotting Time after Food							
		Mean	½ hr.	S.D.	1 hr.	S.D.	2 hr.	S.D.	3 hr.	S.D.
			Mean		Mean		Mean		Mean	
Butter	19	1,029.4	−28.5	10.66	−42.8	12.44	−30.4	13.4	−28.2	15.5
Oleomargarine	19	1,038.9	−15.8	6.82	−23.3	9.90	−16.9	9.4	−18.2	9.9
Difference	..	.....	12.7	.....	19.5	.....	13.5	....	10.0	....
Corn oil	1	1,140	−37.5	.....	−47.3	.....	−26.3	....	−15.7	....
Hydrogenated fat	1	1,140	− 2.6	.....	+15.7	.....	+ 5.2	....	− 2.6	....

feeding fat. In three different groups of patients fed either cream or corn oil the per cent decrease in clotting time at one hour was 40.9, 44.1 and 39.1.[4] The best agreement in values was obtained one hour after feeding the fat. The results at the second hour were quite variable for unknown reasons.

COMMENT

The measurement of whole blood clotting time is an important clinical technic because it is often the test which leads to more definitive studies in patients with defects in coagulation. This test has fallen into disrepute because of the extent of variability of the results. In this paper some of the factors concerned in this variability are discussed. Certain factors, such as a good sharp venipuncture, no foaming, etc., are precise factors in technic which cannot be disregarded without materially affecting the results. Other factors are important but their exact significance is not known. One of these factors is the temperature at which the blood is clotted. In the description of the method 38°c. is stated. This is not a "physiologic temperature" because the blood is exposed to considerable variation in temperature in its passage from skin vessels to deep viscera such as the liver. It is frequency of tilting the tubes. If any factor such as frequency of tilting tubes or in the temperature is changed, a new normal range of clotting time must be established. With the method described a decrease of 30 per cent from a control valve has been considered significant. Some investigators[6] have arbitrarily applied this value to a technic with a normal range twice that of the present method. When a technic is varied, tests of significance must be applied to the new one.

It is usually implied that the variability in studies on blood clotting are due to variations in technic. Circulating blood, however, is a dynamic tissue which is influenced by endogenous and exogenous factors which may alter the constituents of the blood or their reactivity. If variations in these exogenous and endogenous factors are kept at a minimum, and this is best attained in the basal state, whole blood clotting time on a single individual is remarkably reproducible. Some of the exogenous and endogenous factors which may affect the rate of whole blood clotting are variations with menstrual cycle, anxiety, or any factor causing the release of epenephrine, the non-specific stress of mild exercise or exposure to cold and changes in diet. In particular, the oral ingestion of fat accelerates the clotting of whole blood.

Wright[6] and co-workers have reported that they cannot confirm our results and quote to the same effect a personal communication from Schneider and Foley, workers in the same laboratory. In addition, they have attempted to explain the cause of our results as technical artifacts but their published observations do not support the conclusions. Foley[15] fed a meal very rich in fat. It has been long known that one cannot evaluate the effect of fat when a mixed meal is fed. Other ingredients, notably sugar, may inhibit the clot-accelerating effect of fat.

The authors[6] state that in a number of their experiments a tendency was noted for the blood clotting time to return toward the control value after a significant shortening had occurred, and that this same biphasic type of curve is illustrated in one of our graphs. This return toward normal is not a tendency but a constant finding in our studies and appears in all of our published work. The biphasic curve is an integral part of the phenomenon. A biphasic curve means that after feeding fat an accelerated clotting time is detectable within one-half hour and that it reaches its minimum clotting time in one hour. Thereafter the clotting time returns to or toward normal in the second and third hour. If the accelerated clotting time were due to adsorbed thrombin, the clotting in the second and third hour should be even shorter, due to an increased amount of thrombin. The biphasic response cannot be dismissed as possibly due to variations in activity of adsorbed thrombin because the activity of "thrombin" did not decrease in the published experiments[6] of these investigators. Similarly, one must also explain why feeding 10 ml. of water[14] does not produce an accelerated clotting time. The artifact explanation, furthermore, would not explain why in certain disease conditions, observed in fifty-eight patients,[5] there was no accelerated clotting time after cream but often there was a prolonged clotting time. These patients were all studied by the same technic. The only difference was that they had cancer. It would be reasonable to expect an answer to these questions before the results can be dismissed as due to a technical artifact.

Tulloch's[6] failure to find an accelerated clotting time on dilution is unexplainable. All normal plasma gives an accelerated clotting time on dilution to 60 per cent, due to the differential dilution of inhibitors and accelerators and does not depend on the ingestion of fat. A possible explanation for this lack of confirmation of a normal phenomenon is an error in dilution. Tocantins[16] uses the terms "60 per cent" and "30 per cent plasma" because even in whole blood clotting it is only the plasma which clots. If one assumes an hematocrit of 50, Tulloch's 60 per cent blood becomes 43 per cent plasma which may be on the ascending limb of Tocantin's biphasic curve. The authors do not mention what results were obtained with 30 per cent blood (17.6 per cent plasma). This extreme dilution can be used with plasma because the end point of clotting is the moment when fibrin threads become visible. In whole blood clotting these fibrin threads are not detectable, a solid clot usually does not form at this dilution and, if an end point can be determined, the clotting time is prolonged.

Tulloch[6] states that in their experiments with fibrinogen solutions there was no clotting when a silicone-coated syringe was used. He concludes that thrombin is not adsorbed on silicone. The conclusion that thrombin is not adsorbed on a silicone surface is not supported by the results presented or literature quoted.[17] Other explanations are possible in view of the fact that silicone exhibits clot-delaying properties which are independent of its surface effects.[18] Even if the authors[6] are correct, it only lends weight to our results because we obtain the same response to orally ingested fat with a complete silicone technic. (Tables I and III.)

The authors[6] stress their experiments with fibrinogen. This present paper adequately refutes the concept that adsorbed thrombin is a factor in plasma clotting. Even if one assumes that Tulloch's[6] results are significant, their findings do not refute our work. They state that no clotting occurred upon addition of fibrinogen to a syringe which has been used once. After we use a syringe once for control clotting time and draw blood into it one-half hour after cream, an accelerated clotting time is obtained. From Tulloch's work he cannot conclude that this accelerated clotting time is due to adsorbed thrombin. The syringes in which Wright's[6] group obtain most clotting of fibrinogen are ones used four, five and six times. In our experiments the clotting time progressively returns to or toward normal with the fourth or fifth venipuncture. This biphasic response is not explained by Tulloch's experiments.

Wright[2] and Tulloch, Overman and Wright[6] state that our results are due to the employment

of "re-used" syringes. Actually all syringes are "re-used" unless one uses a syringe for only one venipuncture and then destroys it. The problem of "re-used" syringe depends on a definition of adequate cleaning. Adequate cleaning of blood products is secured by washing syringes in running water and rinsing in 0.85 per cent sodium chloride solution. This is proved by the fact that our results reveal a normal clotting time even after four or five repeated venipunctures. Tulloch[6] stresses the point that the syringe should be sterilized by heat. His conclusions are not valid from his experimental evidence because he sterilized one syringe out of nine in this manner. Actually he did not obtain a clot in three out of eight syringes which were not sterilized. The syringe sterilized by heat had an excellent opportunity, by chance alone, not to have a clot. If Tulloch can prove that heat sterilization is necessary, our case is weakened; but so is that of the other investigators doing blood coagulation studies, because if syringes must be sterilized by heat so must the pipettes into which plasma is drawn and in particular the test tubes in which the actual clotting time is measured. Very few investigators, if any, sterilize pipettes and test tubes.

Tulloch, Overman and Wright[6] in studying thirty-one subjects were unable to confirm our result. Nevertheless, from a study of over 1,000 subjects and numerous animal experiments over a five-year period the evidence is that the oral ingestion of fat in the form of olive oil, refined corn oil and cream from cow's milk produces a definite acceleration of the clotting time of fresh whole venous blood in humans and in dogs. The reasons for this statement are as follows: (1) The consistent biphasic character of the response defies explanation as a technical artifact. (2) Control studies in which water was substituted for cream did not result in an accelerated clotting time.[14] (3) The same results are obtained with a sterile syringe for each venipuncture with a switched-syringe technic and with a complete silicone technic. (4) Cream *in vitro* exhibits clot accelerating properties.[14] Pavlovsky[19] has shown that a clot accelerator may be extracted from cream. (5) In the same individual a difference in response is obtained depending on the phase of the menstrual cycle.[10] (6) The changes in clotting time are associated with changes in plasma lipid fractions.[10] (7) The clot-accelerating effect of orally ingested fat may be partially inhibited by the simultaneous feeding of sugar.[4] (8) The response to cream is altered by disease, notably cancer.[5] (9) Not all fats accelerate blood coagulation. It appears that the more saturated the fat, the less effect it has on blood coagulation. (10) The oral ingestion of fat may inhibit the anticoagulant properties of intravenously administered heparin.[20]

SUMMARY

1. Variations in technic of obtaining the sample of blood and in measuring the rate of coagulation are only partly responsible for the variability of the whole blood clotting times.

2. Some of the variability in whole blood clotting times is due to the *in vivo* effect of exogenous and endogenous factors affecting the circulating blood.

3. With a standard technic which is fully described, the rate of clotting of whole blood is remarkably constant in the same individual on the same day or on different days if the individual is studied under conditions which keep the variability of endogenous and exogenous factors at a minimum.

4. The basal state is the best condition in which to study the rate of clotting of whole blood because the variations in endogenous and exogenous factors are at a minimum.

5. Ingested fat in the form of cream or butter accelerates the rate of coagulation of whole blood. The response is detectable in one-half hour after ingesting the fat and reaches a maximum in one hour. Thereafter, the effect progressively diminishes. This results in a constant and characteristic biphasic curve of response.

6. The accumulation of thrombin on glass does not explain this phenomenon.

7. The term "re-used" syringes is defined and evidence is presented that adequate washing in running water and saline permits the "reuse" of a syringe without influencing the results.

8. Sterilization of syringes, pipettes and test tubes which are used in measurements of the rate of blood coagulation is unnecessary.

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Review

Primary Thrombosis of the Internal Carotid Artery*

Report of Seven Cases with Cerebral Circulatory and Metabolic Studies

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In 1914 Hunt[1] presented a remarkably clear description of the clinical syndromes that may occur as the result of obstruction of the carotid artery and its major branches. He suspected that spontaneous, non-traumatic thrombosis of these vessels occurred more commonly than was realized, and he stated the belief that more careful examination of the vessels in the neck during life and at the autopsy table in all cases presenting cerebral symptoms would reveal its presence more often than was recognized at that time. However, little or no progress was made in the recognition of spontaneous internal carotid artery thrombosis until 1937 when Moniz,[2] by means of cerebral angiography, demonstrated previously unsuspected thrombosis of the internal carotid artery in four patients. Since then greater interest in the subject has been evident and a number of case reports and reviews have appeared.[3–16] From these studies have emerged certain features, unknown to Hunt, concerning age and sex incidence, site of thrombosis, etc., but little has been added to his description of the clinical neurologic syndromes that may occur.

Present knowledge of the subject may be briefly summarized as follows:

Etiology: Atherosclerosis appears to be the most common cause for primary thrombosis of the carotid arteries, although the number of reported cases in which the vessels have been examined histologically is relatively small. Various other underlying etiologic factors have been reported and considered, including thromboangiitis obliterans, periarteritis nodosa, temporal arteritis, syphilis, congenital aneurysms of cerebral vessels with extension of a thrombus into the internal carotid, tumors in the neck, mild and overlooked trauma, polycythemia vera, etc. Such factors may occasionally account for the lesion under discussion but the evidence to date clearly indicates that atherosclerosis is most often responsible for spontaneous thrombosis of the carotid artery and its major branches.

Age and sex incidence: The condition has been reported from the first through the eighth decades of life, with a preponderant distribution between the fourth through the seventh decades. For unknown reasons males are affected more frequently than females.

Site of involvement: The left internal carotid artery is more frequently involved by spontaneous thrombosis than is the right, by a ratio of 3 to 2 according to Gurdjian and Webster.[15] Whether this predominance of incidence on the left is the result of anatomic or other factors is undetermined.

Clinical syndromes: There are four reasonably well defined clinical syndromes that may be associated with spontaneous thrombosis of the carotid arteries in the neck: (1) The onset of symptoms may be sudden and acute, in which case the clinical picture usually closely simulates that of an intracerebral vascular lesion. Careful palpation of the vessels in the neck may provide the clue to the extracerebral location of the lesion. (2) The onset of symptoms may be insidious with transient episodes of visual dis-

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turbances, hemiplegia, monoplegia, aphasia, etc., with a slowly progressive course over a period of months or years; a course which may closely resemble that of an expanding intracranial lesion. Under these circumstances the correct diagnosis has often been made by cerebral arteriography after initial studies of the cerebrospinal fluid and the ventricular system by air injection have failed to demonstrate an intracranial mass. (3) If a thrombus in the internal carotid artery extends to involve and occlude the ophthalmic artery, homolateral blindness and contralateral hemiplegia may result. This combination of signs should immediately direct attention to the extracranial location of the lesion. (4) Thrombosis of the internal carotid artery may occur silently without significant disabling or localizing signs.

In each of the clinical syndromes referred to, the course of the disease may be complicated by recurrent episodes of syncope. Galdston, Govons, Wortis, Steele and Taylor[5] found the contralateral carotid sinus to be hyperactive and the homolateral carotid sinus insensitive in two subjects with internal carotid artery thrombosis. Whether there is a cause-and-effect relationship between the vascular occlusion and the abnormal function of the carotid sinus reflex or whether the relationship is simply one of chance is uncertain. In any event the carotid sinus mechanism is not the only and probably not the most important factor involved in the causation of syncope when it occurs in subjects with this disorder. Since the brain is dependent upon the patency of a single artery for the major proportion of its blood supply, any interference with blood flow through that vessel may result in cerebral ischemia of sufficient degree to cause syncope. External pressure, whether applied over the carotid sinus or at any other point over the course of the common carotid artery, may thus precipitate syncope. The potentially harmful effects upon the brain of contralateral common carotid artery compression when an internal carotid artery is occluded are the same as those of stimulation of a hyperactive carotid sinus and the same care and precautions should be taken when the common carotid artery is compressed as are observed when the carotid sinus is stimulated by massage.

The purpose of the present communication is to report seven cases of primary thrombosis of the internal carotid artery, with the results of studies of cerebral hemodynamics and metabolism in each. In one of the patients a common carotid-internal jugular vein anastomosis was established on the side of the thrombosed internal carotid in an attempt to increase the supply of arterial blood to the brain. The results of studies made before and after this procedure are included in this report.

METHODS

The cerebral blood flow (CBF) was determined by the nitrous oxide method. For the first two subjects (S. S. P. and A. R. S.) the original procedure of Kety and Schmidt[17] was employed; for the remainder of the subjects the Scheinberg and Stead[18] modification of the original method was used. Cerebral oxygen consumption ($CMRO_2$) was calculated from the CBF and arterial-cerebral venous oxygen difference. The mean arterial blood pressure (MABP) was measured directly from a peripheral artery with a damped mercury manometer. The cerebral vascular resistance (CVR) was calculated from the CBF and the MABP. Blood oxygen content and carbon dioxide content were determined manometrically.[17]

The circulatory studies were performed in each subject during a chronic phase of his illness when the course of the disease had become either stationary or its progression reduced to a very slow rate. None of the studies reported were carried out during an active phase of rapidly changing neurologic signs.

CASE REPORTS

CASE 1. S. S. P., a fifty year old white man, was admitted to the hospital on November 4, 1949, with a complete left hemiplegia of thirty-six hours' duration. Progressive personality changes characterized by increasing irritability, undue suspicion and unprovoked outbursts of temper had been noted by the patient's family during the eighteen months prior to the onset of hemiplegia. For one year the patient had complained of frontal and occipital headaches of gradually increasing frequency and severity. Several transient episodes of left hemiparesis lasting from a few minutes to two hours had occurred during the three months prior to hospitalization.

The pertinent physical findings on admission consisted of a left hemiplegia with a left central facial paralysis, complete loss of cortical sensory function on the left and a left homonymous hemianopsia.

Spinal fluid examination and pneumoencephalograms failed to demonstrate evidence of brain tumor. Cerebral arteriogram showed the internal carotid artery to be completely obstructed 1 cm. distal to the bifurcation of the right common carotid artery, and surgical exploration of the right common carotid artery at its bifurcation confirmed these findings. On January 19, 1950, a side-to-side anastomosis of the right common carotid artery and the right internal jugular vein was performed. The cerebral angiogram was repeated fourteen and twenty-seven days after operation and on neither occasion was contrast material observed to enter the lateral or sagittal venous sinuses. Over an eighteen-month period of observation the course of the disease did not appear to have been altered either in terms of rate or of degree of return of function. Consequently, the circulatory pathways in the neck were surgically restored to normal. A year later, in November, 1952, the patient died following the development of the syndrome of pseudobulbar palsy.

At autopsy an old organized thrombus was found in the right internal carotid artery along with widespread encephalomalacia of the right cerebral hemisphere. In the left internal carotid artery a more recent, organizing thrombus was found. Several small, more recent areas of encephalomalacia were present in the left cerebral hemisphere, in association with the presence of emboli in several of the smaller branches of the left middle cerebral artery. The vessels at the base of the brain, other than the internal carotids, were involved by minimal atherosclerotic changes.

Comment. The chronicity and progressive character of the clinical course in this patient led to an initial diagnosis of brain tumor. When the initial studies failed to confirm this the correct diagnosis was established by cerebral angiography. A common carotid artery-internal jugular vein anastomosis was surgically established in an unsuccessful attempt to by-pass the obstruction in the internal carotid artery and to increase the vascularity of the brain. The circulatory pathways in the neck were subsequently restored to normal. A year later the patient died when a thrombus formed in and occluded the left internal carotid artery.

TABLE I

CEREBRAL HEMODYNAMICS AND METABOLISM FOLLOWING SPONTANEOUS INTERNAL CAROTID ARTERY THROMBOSIS

Case No. and Patient	Mean Arterial Blood Pressure (MABP) (mm. Hg)	Cerebral Blood Flow (CBF) (cc./min./ 100 gm.)	Cerebral Vascular Resistance (CVR) (mm. Hg/cc./min./ 100 gm.)	Cerebral Oxygen Consumption ($CMRO_2$) (cc./min./ 100 gm.)	Arterial-cerebral Venous Oxygen Difference ($A\text{-}Vo_2$) (vol. %)	Cerebral Oxygen Extraction Ration (ERo_2) (%)
I, S. S. P.	98	44	2.2	2.7	6.13	35
II, A. R. S.	103	29	3.6	2.9	9.96	53
III, G. I. C.	103	57	1.8	3.2	5.60	31
IV, H. P. C.	106	39	2.7	2.9	7.41	38
V, A. S. P.	107	47	2.3	2.8	5.94	29
VI, A. D.	97	38	2.6	3.2	8.5	34
VII, O. P. J.	85	53	1.6	3.2	6.02	36

The results of the cerebral circulatory studies in this subject are summarized in Table I. When they are compared with the mean values for these functions in healthy young males, as reported by Kety and Schmidt[17] using the original multiple sample method, the CVR is found to be increased and the CBF reduced. The 38 per cent increase in CVR is partially compensated for by a slight increase in MABP; CBF is decreased by 19 per cent. $CMRO_2$ is reduced proportionately (18 per cent) as a consequence of the failure of the brain to increase its extraction of arterial O_2 as the blood flow declined.

These studies could not be repeated after creation of the arteriovenous fistula because of contamination of cerebral venous blood in the intact internal jugular vein by arterial blood from the A-V shunt on the opposite side. However, measurements of the arterial-internal jugular venous oxygen difference were made twelve days, forty days and five months after

operation. These findings are summarized and are compared with preoperative findings in Table II. The arterial-cerebral venous oxygen difference before operation is normal. The rise in internal jugular venous oxygen content and decrease in A-V_{O_2} following operation is the result of contamination of internal jugular venous blood by arterial blood from the A-V shunt on the opposite side.

CASE II. A. R. S., a fifty-five year old white man, was admitted to the hospital on March 14, 1950, in severe congestive heart failure. Eight years prior to admission he had noted a large blind spot in the field of vision of the right eye, and for three months before admission a gradually progressive weakness of the left upper extremity had occurred. Neurologic findings upon admission were: paresis of the left upper extremity, impairment of light touch, pain and temperature appreciation over the ulnar surface of the left hand, and an area of chorioretinitis in the right optic fundus.

On the twelfth hospital day there was a sudden decrease in visual acuity in the right eye. During the succeeding ten days a complete left hemiplegia developed and he became irrational and confused. On April 10, 1950, complete obstruction of the right internal carotid artery just beyond its origin was demonstrated by cerebral angiogram. The heart failure was refractory to treatment and the patient died two months after admission to the hospital.

At autopsy the right internal carotid artery was found to be occluded by a well organized, adherent thrombus which had extended into the middle cerebral artery and occluded its frontal, central and parietal branches. The remainder of the cerebral arteries were patent and only moderately arteriosclerotic.

Comment. The results of cerebral circulatory studies in this subject are summarized in Table I. Although the increase in CVR (125 per cent) and the reduction in CBF (46 per cent) is greater than occurred in the first subject, $CMRO_2$ in contrast is maintained at a nearly normal rate by a large increase in A-V_{O_2}. These changes are identical with those that accompany congestive heart failure alone.[21] The contribution of the internal carotid artery occlusion to the circulatory derangements in this subject could not be defined, since the heart failure was refractory to treatment and compensation was never attained. The probable sequence of events, however, is as follows: (1) The thrombus occurred, silently except for a visual field defect, eight years ago and was accompanied by an increase in CVR[29] without significant change in cerebral function until congestive heart failure supervened. (2) The progressive increment in CVR incident to the development of refractory congestive heart failure eventually reduced the CBF to the point where it was insufficient to maintain the structural integrity of the whole brain. (3) Extension of the thrombus into the middle cerebral artery occurred terminally and was responsible for the late neurologic manifestations.

TABLE II
CASE I, S. S. P.
ARTERIAL-CEREBRAL VENOUS OXYGEN DIFFERENCE BEFORE, AND ARTERIAL-INTERNAL JUGULAR VENOUS OXYGEN DIFFERENCE AFTER ESTABLISHMENT OF THE COMMON CAROTID-INTERNAL JUGULAR ANASTOMOSIS

Date	Arterial O_2 Content (vol. %)	Internal Jugular Venous O_2 Content (vol. %)	Arterial-internal Jugular Venous O_2 Difference (vol. %)
1-19-50 (preoperative)	17.27	11.14	6.13
1-31-50 (12 days postoperative)	16.38	14.55	1.83
2-28-50 (40 days postoperative)	16.30	13.15	3.15
6-23-50 (5 months postoperative)	16.70	13.81	2.89

CASE III. G. I. C., a sixty year old white man, entered the hospital July 11, 1950. During the preceding five years he had had frequent syncopal episodes; the attacks usually were precipitated by specific body motions, such as bending forward from the erect position or by turning the trunk from right to left. One year prior to admission he had had a "mild stroke," characterized by aphasia, paresthesias and motor weakness of the right side of the face and right upper extremity. The aphasia and paresthesias subsided after twenty-four hours but mild weakness of the right upper extremity persisted. Except for slight motor weakness in the right upper extremity, there were no neurologic abnormalities. The characteristic physical signs

of aortic stenosis were present, but the heart was not enlarged, and there was no evidence of cardiac insufficiency. Compression of the neck in the region of the right carotid sinus resulted in cardiac asystole and syncope; pressure over the left carotid sinus had no effect. Upon subsequent examination it was demonstrated that syncope could be induced as readily by compression of the right common carotid artery below its bifurcation as by pressure applied directly over the carotid sinus. The diagnosis of thrombosis of the left internal carotid artery was made on the basis of these findings and was confirmed by cerebral angiography.

Comment. The results of cerebral circulatory studies in this subject are summarized in Table I. CBF, CVR, $CMRO_2$ are well within the normal range of values for these functions in subjects in this age group. These findings and the absence of important neurologic sequelae in this subject illustrate the benign cerebrovascular effects of unilateral internal carotid artery occlusion when total CVR is normal. However, when the integrity of the cerebral circulation is dependent upon the patency of a single internal carotid artery, acute cerebral ischemia and syncope may result from otherwise minor and quickly compensable disturbances in the general circulation. The response to unilateral compression of the common carotid artery below its bifurcation and the carotid sinus is a useful procedure in the clinical recognition of primary thrombosis of the internal carotid artery. The induction of syncope by this maneuver may be considered as strong presumptive evidence of occlusion of the contralateral internal carotid artery.

Case IV. H. P. C., a sixty-two year old obese white salesman, was admitted to the hospital on September 26, 1952, because of paresthesias of the right upper extremity for three months, mental confusion and a right central facial paralysis for three weeks, and complete right hemiplegia and motor aphasia for two weeks. A cerebral arteriogram had been obtained at another hospital and had shown the left internal carotid artery to be occluded just distal to its origin from the common carotid artery. In addition to the neurologic findings, it was noted that momentary syncope could be induced by exerting gentle external pressure over the right common carotid artery in the neck.

For one month after the institution of physiotherapeutic measures there was gradual and progressive clinical improvement; however, the patient died forty-eight hours after the sudden onset of left hemiplegia and the syndrome of pseudobulbar palsy.

Pertinent findings at autopsy were (1) encephalomalacia of the left parietal cortex, right internal capsule and right basal ganglia, (2) marked atherosclerosis of both internal carotid arteries, each of which was occluded by a thrombus (the thrombi were of different ages, the one on the right being fresh and of more recent origin), (3) except for the internal carotid arteries the walls of the cerebral arteries were soft, pliant and translucent.

Comment. The cerebral circulatory studies in this subject, the results of which are summarized in Table I, were made shortly after he was admitted to the hospital, when the right internal carotid artery was patent. As a consequence of the large increase in CVR (100 per cent), which is only partially compensated for by the small increase in MABP, CBF is reduced by 40 per cent. The reduction in CBF is, on the other hand, more completely compensated by the increase in cerebral O_2 extraction ($A\text{-}V_{O_2}$, 7.41 vol. per cent) so that $CMRO_2$ is only moderately decreased.

The autopsy findings in this case indicate that the abnormally high resistance to the flow of blood to the brain was imposed by obliterative atherosclerosis of both internal carotid arteries. The intracerebral vessels, the lumen diameter of which usually determines CVR, were normal. Although studies to determine the effect of cerebral vasodilating and constricting agents were not made, it seems quite unlikely that such agents could have influenced CBF, for it may be reasonably assumed that the extremely sensitive intrinsic mechanisms that normally regulate and maintain CBF are rendered ineffective by these circumstances.

Case V. A. S. P., a fifty-nine year old white man, was referred to the hospital on March 2, 1952, with a provisional diagnosis of an expanding lesion of the brain. During the preceding two months he had experienced intermittent and transient episodes of paresthesias in the left upper extremity. Three weeks before admission one of these attacks had lasted for two hours and involved both upper and lower extremities on the left side. He was free of neurologic symptoms or signs in the intervals between these episodes; however, four days prior to admission there was abrupt onset of a complete left hemiplegia and motor aphasia. Physical examination

revealed a semi-stuporous white male with a left hemiplegia and hemianesthesia, a left central facial paralysis, and motor aphasia. After initial studies had failed to confirm the presence of an expanding intracranial lesion, the correct diagnosis was established when a cerebral angiogram showed the right internal carotid artery to be occluded at a point 3 cm. distal to the bifurcation of the common carotid artery.

Comment. The results of the cerebral circulatory studies are summarized in Table 1. The 77 per cent increase in CVR and moderate increase in MABP is accompanied by a 26 per cent reduction in CBF. $CMRO_2$ is diminished in proportion to the decrease in CBF, since no increase in cerebral oxygen extraction occurred.

Case vi. A. D., a fifty-two year old white male farmer, entered the hospital on May 13, 1952, a few hours after he had been found lying upon the floor of a hotel room. He was conscious but unable to move the right arm or leg, or to talk. Although it was not possible to obtain a reliable account of his illness from the patient, it appeared that he had been in reasonably good health until two weeks before admission, during which time the only known symptom suggesting vascular disease had been the occurrence of nocturnal paresthesias of the lower extremities. Upon physical examination, however, there was evidence of widespread occlusive vascular disease. The pulsation of the internal carotid artery could be easily palpated on the right but was absent on the left side; the femoral pulsation on the right was absent and there was early gangrenous demarcation in the leg at mid-thigh level. The neurologic findings consisted of motor aphasia and right-sided hemiplegia and hemianesthesia. Funduscopic examination revealed pallor of the left retina and arteriolar segmentation.

Surgical amputation of the right lower extremity became necessary when the limb failed to respond to conservative measures. Examination of the surgical specimen revealed no evidence of vascular disease other than obliterative atherosclerosis. There has been little or no change in the neurologic findings, in spite of intensive physiotherapeutic efforts.

Comment. Although the diagnosis of internal carotid artery occlusion was not confirmed by angiography in this case, it is strongly supported by the clinical findings: absence of the left internal carotid artery pulsation, right hemiplegia, and pallor, with arteriolar segmentation in the left optic fundus. An unusual clinical feature is the simultaneous or nearly simultaneous occurrence of thrombi in two large arteries in widely separated regions of the peripheral arterial tree.

The results of the cerebral circulatory studies are summarized in Table 1. Cerebral vascular resistance is increased (100 per cent); cerebral blood flow reduced (40 per cent); cerebral oxygen utilization is maintained at a nearly normal rate by an increase in cerebral oxygen extraction ($A\text{-}V_{O_2}$ 8.5 vol. per cent).

Case vii. O. J., a thirty-seven year old white man, was admitted to the hospital ten days after the onset of weakness in the left arm and left side of the face. He had been previously well except that he had noted some impairment of memory during the preceding years.

The pertinent findings upon examination were: lethargy, a left central facial weakness, spastic paresis of the left upper extremity, and adiadokokinesis of the left hand. Study of the visual fields revealed a left homonymous hemianopsia. X-rays of the skull and spinal fluid studies were normal. Cerebral arteriogram showed that the right internal carotid artery was occluded at a point 1 cm. from its origin. This finding was confirmed by surgical exploration. There was rapid improvement in the neurologic findings after institution of a program of physiotherapy.

Comment. The results of the cerebral circulatory studies are summarized in Table 1 and show no important deviation from the normal. When compared with the mean values of normal males in this age group, the CBF is slightly reduced, CVR slightly increased and CMRO, moderately reduced; the values, however, fall well within the range found by Madison and Sensenbach[22] in healthy males in the fourth decade of life.

DISCUSSION

It is apparent that non-traumatic thrombosis of the internal carotid artery occurs with greater frequency than has been generally recognized in the past. Since the advent of the technic of cerebral angiography, a better understanding of the clinical features of internal carotid artery occlusion has evolved, and numerous reports[3–16] during the past few years have demonstrated that it often can be recognized clinically and differentiated from intracranial vascular and neoplastic lesions whenever these features are

given proper consideration. The ocular manifestations that may accompany internal carotid artery occlusion which, in addition to homolateral blindness include hemianopsia, pupillary changes, ophthalmoplegia and optic atrophy have been emphasized recently[23–25] and Milletti[26] has reported that internal carotid artery occlusion is accompanied by a homolateral decrease in systolic retinal tension. He further found that compression of the carotid artery in the neck on the side of the occlusion does not alter retinal tension in either eye whereas compression of the contralateral artery results in a bilateral fall in systolic retinal tension. The response of the state of consciousness of a subject to external compression of the common carotid artery in the neck, first on one side and then on the other, may also provide information of diagnostic value, for when momentary syncope can be induced by external compression of the common carotid artery in the neck (below the carotid sinus) on one side and has no effect on the opposite side, a presumptive diagnosis of internal carotid artery occlusion may be made with a high degree of certainty. The diagnostic value of this maneuver has been demonstrated in two of the seven subjects of this report.

Another feature of the present series that is worthy of mention is the fact that the cause of death in two of the three patients who died was thrombosis of the opposite internal carotid artery. Although the morbidity of unilateral internal carotid artery occlusion is relatively high in the older age groups, the mortality rate appears to be low. Most patients survive unilateral internal carotid artery thrombosis; but the findings in this small series suggest that death due to subsequent thrombus formation in the opposite internal carotid may occur more often than has been previously realized.

The results of the cerebral circulatory studies made in these seven patients reveal no hemodynamic or metabolic changes that can necessarily be attributed to occlusion of the internal carotid artery. The decrease in CBF, increased CVR and moderate reduction in $CMRO_2$ that occurred in five of the seven patients are similar to the changes in cerebral hemodynamics and metabolism that have been shown by Fazekas, Alman and Bessman,[19] Frehyan, Woodford and Kety,[27] Scheinberg,[20,28] Madison and Sensenbach[22] to accompany a variety of conditions, including the aging process, cerebral arteriosclerosis and congestive heart failure. In later decades of life, even in the absence of clinical evidence of cerebral arteriosclerosis, CVR may be increased, CBF reduced and $CMRO_2$ moderately decreased. In the presence of known cerebrovascular disease, there is progressive increase in CVR and reduction in CBF; $CMRO_2$ is initially maintained by a compensatory increase in cerebral O_2 extraction but as the vascular disease becomes more severe and the CBF further declines, $CMRO_2$ may also fall. Thus the changes observed in the group of patients under consideration here do not differ from those of similar age groups without internal carotid artery occlusion. In two of the patients, the youngest, Case VII, age thirty-seven, and one of the oldest, Case III, age sixty, the cerebral circulatory and metabolic functions were within the normal range.

In a study of the effect of unilateral carotid artery ligation upon cerebral hemodynamics, Shenkin, Cabieses, Van Den Noordt, Sayers and Copperman[29] found that the CVR is increased after this procedure. No change in CBF and no neurologic complications occurred in three patients in the younger age group (fifteen, eighteen, twenty-five years) in whom the CVR was normal before ligation; reduction in CBF and hemiplegia developed in the patient, age fifty-three, of the series in whom the CVR was abnormally high before ligation. In each of the subjects with internal carotid artery thrombosis in whom extensive and irreversible neurologic sequelae occurred, the CVR after the occlusion had occurred exceeded 2.2 mm. Hg/cc./100 gm./min., and the CBF was moderately to markedly reduced; while the neurologic sequelae that occurred in the two subjects in whom CBF was normal, and CVR only slightly increased (1.6 and 1.8 mm. Hg/cc./100 gm./min.) after occlusion, were minimal and in one of the two cases was completely reversible. These studies suggest that cerebral circulatory studies should be done, whenever feasible, prior to therapeutic carotid ligation for they may provide important and otherwise unobtainable information regarding the safety of the procedure.[30,31] It is perhaps likely that carotid ligation may be performed without undue risk of neurologic sequelae in individuals in whom the cerebral vascular resistance is normal; on the other hand, significant and irreversible neurologic complications may be expected to occur when carotid ligation is attempted under circumstances in which there is a pre-existing increase in CVR.

There is no effective means for the treatment of internal carotid artery thrombosis. The use of anticoagulants is not beneficial and such measures as stellate ganglion block, stellate ganglionectomy and surgical resection of the thrombosed segment of the artery have been unsuccessful. In 1949 Beck[32,33] suggested that revascularization of the brain might be accomplished by establishment of a cervical arteriovenous fistula. A common carotid artery-internal jugular vein anastomosis was created on the side of the occluded internal carotid artery in Case 1, S. S. P., in the hope of accomplishing this end. However, postoperative studies of the oxygen content of blood from the opposite internal jugular vein in the patient indicated that the chief effect of the fistula was to divert the stream of arterial blood from the carotid artery by way of the internal jugular vein to the transverse sinus on the same side, into the transverse sinus of the opposite side, and thence to leave the skull by way of the opposite internal jugular vein. The studies of Gurdjian, Webster and Martin[35] in monkeys, Hammer, Heersma, MacGregor, Dew and Osius[34] in children, and the angiographic studies of Tarlov, Shure, Epstein, Hirsh and Nissen[36] and of Gurdjian, Webster and Martin[37] further testify to the ineffectiveness of this procedure in increasing the vascularity of the brain. After eighteen months, during which time no change in the neurologic status of the patient occurred, the circulatory pathways in the neck were restored to normal.

SUMMARY

The literature on spontaneous internal carotid artery thrombosis is reviewed and seven additional cases are reported. The clinical characteristics of the disorder are discussed, with special reference to those features which are of particular importance with respect to clinical recognition.

Cerebral circulatory studies made in these seven patients did not reveal hemodynamic or metabolic changes that could be convincingly attributed to unilateral internal carotid artery thrombosis alone. However, the studies of others[30] have shown that interruption of the flow of blood through one internal carotid artery is accompanied by an increase in CVR. Our results indicate that neurologic sequelae in internal carotid artery thrombosis occur only when this increment in CVR is superimposed upon a pre-existing increase in CVR which is of sufficient magnitude to reduce CBF to a level which is insufficient to maintain the structural integrity of the entire brain. They emphasize the fact that it is the state of the CVR prior to internal carotid artery occlusion that determines whether neurologic complications will occur. It is suggested that cerebral circulatory studies should be done, whenever feasible, before therapeutic carotid artery ligation, for they provide important and otherwise unobtainable information regarding the safety of the procedure.

In one of the patients an attempt was made to revascularize the brain by creating an artificial common carotid artery-internal jugular vein fistula on the side of the thrombosed internal carotid artery. Postoperative cerebral angiograms and studies of arterial-internal jugular venous oxygen difference showed this procedure to be ineffective.

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Seminars on Antihypertensive Drugs

Management of Hypertensive Disease*

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Concepts of management of hypertensive disease have changed radically within the memory of most. From an impotent concern with the expectant care of its sequelae, we now have to select between a proper expectancy and the use of a variety of more or less active antipressor agents and methods. It would be a pity if the frequent effectiveness of some of these concealed their basically empirical nature or gave support to the notion that the need for truly rational programs of treatment is less acute than ever. We still face the fact that "The same things are not proper for all; . . . a casual trial may perform that which a rational process cannot" (Celsus).

The purpose of this paper is to relate experiences with some of these agents. In using them, two axioms come to mind. The one imposes the duty that treatment should, above all, do no harm; the other suggests that disease should be countered in its incipience, since to delay too long may be to treat too late. The dilemma these axioms pose is resolved by defining the general aim of treatment; this is the maintenance of *average* arterial pressure within ranges consistent with forestalling or ameliorating hypertensive vascular disease. A more precise definition can be made only in terms of the individual and his response to arterial hypertension. The fact that arterial hypertension as such is a major factor in the progression of hypertensive vascular disease is not countered by the course of some people who tolerate hypertension very well. For one thing, the average sustained pressures of these remarkable Aunt Maggies may not be so high as their clinical records suggest. Thus, while any vigorous program of treatment may be unnecessary, as well as costly and discommoding in some, in others procrastination may permit irreparable damage.

Early Essential Hypertension. Hypertension, whether of long or short duration, can be considered early when it has not elicited disability or signs of vascular damage. In this situation time is available to follow the course of the disease, to estimate its progress and to determine the response to simple measures.

Mere establishment of the patient's confidence has a well documented therapeutic effect.[1] It is also helpful that he understand something of his disease and realize that he is so constituted that his heart and vessels respond excessively to the slings, arrows and even to the minor discomforts of fortune. These he cannot always avoid; he can, however, reduce their impact by combining charitable acceptance with self control. The ordinary rules of physical and mental hygiene must be his guides, since he pays so heavily for infringing on them.

The most widely—possibly the most wisely—used crutch in this program is the familiar ¼ or ½ gr. of phenobarbital. The makers suggest that the preparations of Rauwolfia serpentina should be tried, arguing that they are harmless, that they promote a more desirable effect than phenobarbital and, especially, that they are specifically depressor. These arguments have some merit; however, the ultimate harmlessness of long-term medication with rauwolfia is not as well established as is that of small dose phenobarbital therapy; further, side effects are sometimes more disturbing and the effect on blood pressure always uncertain.

The decision to undertake active antipressor treatment depends first on the failure of simpler measures and then on age. Sustained hypertension at twenty or twenty-five is more ominous than like hypertension thirty years later.

A more clean-cut prescription would be desirable, but it will require better drugs and a sharper insight into basic mechanisms than we have now. In the meantime, unnecessary treatment at the behest of the advertisers will only generate disappointment and discontent.

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Severe Essential Hypertension. This is hypertension which has resulted in signs and symptoms of vascular damage or in disabilities which demand relief. The relative effectiveness of therapeutic regimens can be objectively demonstrated in these patients, and the advantage of medication is easily gauged against its cost or possible harm. This is particularly true in those who manifest the syndrome of malignant hypertension. For these reasons, our experience is primarily in this aspect of hypertension disease.

Thiocyanate. Many still utterly reject it. However, we are convinced of its value in the symptomatic treatment of hypertensive headache. The mechanism of its action is not known. Its indirect effect of increasing sodium excretion[2] is probably not an explanation of its effectiveness in headache; it is only feebly depressor and this perhaps because it is slightly sedative. The usual warnings must be constantly reiterated against the use of thiocyanate without regular determinations of serum concentration. The combination of small doses of thiocyanate with small doses of phenobarbital sometimes gives symptomatic relief at serum thiocyanate concentrations of 6 mg. per 100 ml. or less and such a routine has the advantage of requiring fewer blood analyses. Intravenous injection of thiocyanate in a dose of 1.0 gm. of the ion yields, in a patient of average size, a serum level of about 6 mg. per 100 ml.; in some it relieves headache within an hour or two and is a useful way of starting on a program of oral administration.[3]

Nitroprusside. The properties of this agent have been noted elsewhere.[4] In brief, sodium nitroprusside is a potent and useful vasodepressor when infused intravenously in doses of 100–400 μg. per minute; the infusion can be continued for many hours and is especially useful in the control of hypertensive encephalopathy. The active agent probably is the nitroso (NO) radicle. Nitroprusside ion itself is rapidly broken down upon contact with tissues, apparently by interaction with sulfhydryl groups; the cyanogen released is detoxified to thiocyanate. Consequently oral medication with nitroprusside is apparently a roundabout way of giving thiocyanate.

Veratrum. Our experience with the veratrum preparations has been less fortunate than that of others. No advantage of the alkaloid, protoveratrine, has been defined over the mixture of alkaloids in veriloid®. A large proportion of patients did not respond by decreased arterial pressure to tolerated doses of either; the majority of those who did soon lost this ability over the course of a few weeks or months, usually because of a progressive narrowing of the margin between emetic and pressor doses.

Since emesis seemed to be a major limiting factor, the effects of veriloid or protoveratrine were tested in eight patients with severe or malignant hypertension who were given thorazine® as an anti-emetic. The experience in this small group exemplifies that in the larger series given veratrum drugs alone. Of the eight, only three responded initially by satisfactory decreases of arterial pressure; two of the three lost most of the vasodepressor effect of veratrum over the course of two to four months, and showed recurrence of the signs of advancing vascular disease. At the end of six months one patient, who has not been troubled by emesis, continues medication with signs of continued responsiveness. In these patients, as in experimental veratrum emesis in dogs, thorazine was at most only slightly anti-emetic.

Hydralazine (1-hydrazinophthalazine). In spite of its wide use and frequent study, the mechanism of action of this drug is curiously obscure and variously interpreted. Its major hemodynamic effects seem to be exerted through central nervous system mechanisms.

Our further experience has been reported.[5] In summary, fifty-four patients were maintained on the drug for fifteen to thirty months because they had shown during treatment reduction of average diastolic pressure to levels under 110 mm. Hg and were therefore classed as responders. The thirty-two others in the group had been given the drug but failed to show this response four to eight weeks at maximum tolerated dosage. The dose was slowly increased to 800 mg. daily or any lower effective level; this dose was maintained for several weeks and then slowly decreased to the minimum consistent with the desired hypotensive effect. Tolerance was not a large problem, since only three of the fifty-four who took the drug for long periods lost their responsiveness to it.

Control and initial observations during therapy were made in hospital, where most were re-examined at intervals. Nearly all were supervised during frequent outpatient visits and the responses were also followed from daily records of home pressure. Results were evaluated in terms of a numerical severity index which was based on assigning four points each to levels of arterial pressure and estimates of cardiac, renal

and cerebrovascular status. In this term, responsiveness to the drug was not a function of the severity of the disease, which was roughly equal in responders and non-responders. Rather, responses were more common in patients whose hypertension seemed, on clinical grounds, primarily neurogenic, and were uncommon in patients whose hypertension was primarily renal or complicated by chronic renal disease.

A favorable response of diastolic pressure was associated with decreases in the estimates of cardiac, renal and cerebrovascular impairment; these functions, after the more rapid initial improvement, still tended to improve slowly thereafter. The advantage gained by the responders was especially evident in their mortality, which was three in fifty-four as compared with eleven among the thirty-two non-responders.

The side-effects of the drug are frequent and familiar. Close supervision is required, especially in patients with arteriosclerotic heart disease and angina pectoris. Strict sodium restriction may be necessary during the initial stages of treatment in older patients. Much more disturbing than the usual transitory and controllable side effects is the rheumatic and febrile syndrome[6] which was observed in several patients, including two of the fifty-four responders in the study group. This seems to be a function in part of dosage and time, since it occurred in patients receiving large doses (about 600–800 mg. daily) for long periods, a fact which indicates the desirability of minimum maintenance dosage.

The initial manifestations of the syndrome resembled incipient rheumatoid arthritis and the febrile form of the ailment was apparently an intensification of this process with pleural and pericardial serositis and "rheumatic" pneumonia. The condition was associated with increased erythrocyte sedimentation rate, and altered distribution of serum proteins consisting of increased gamma globulin and decreased albumin concentrations. The plasma "L.E." tests were positive in some and L.E. cells were found in the marrow of others. Cutaneous manifestations in a few increased the resemblance of the condition to systemic lupus erythematosus. However, with the exception of one patient whose outcome is uncertain,* the renal disease associated with systemic lupus erythematosus has not been seen in these patients; furthermore, the process has responded to discontinuing the drug in most and to decreased dosage in a few, while remission was elicited or accelerated in three patients by courses of ACTH and cortisone. Recovery is apparently complete in most.

The experience shows that hydralazine is an effective antipressor agent in about half of the patients treated and that the great majority of those who respond to it can continue to take it for long periods, with sustained slow improvement in cardiovascular status. Its frequent initial side-effects and the delayed toxic responses seen in a few who continue large doses for long periods restrict its use to patients demonstrably suffering from hypertensive vascular disease. Still, taking these into account, hydralazine continues as an outstanding advance in the treatment.

Hexamethonium. Our experience with this drug can be considered in more detail since it has not been described elsewhere.

We had hoped that sustained partial blockade of sympathetic transmission might help define those patients whose hypertension is primarily sustained by neural mechanisms. Further, as the study began, the value of hexamethonium was variously considered sometimes from results of brief study of small groups[7] or from its use in association with other drugs. To these, Smirk's extensive evaluation and generally favorable conclusions were exceptions.[8] Lastly, a combination of hydralazine with hexamethonium was reported[9] as rather uniformly effective in severe hypertension.

One group of patients was treated with hexamethonium or a like agent (pendiomid®) alone and another group with hexamethonium and hydralazine in combination and separately.

Results were evaluated in terms of changes in a composite severity index which is a simplification of that used in former hydralazine studies. The index is designed to express numerically the over-all severity of the patient's disease at the time of observation by assigning a maximum of four points each to estimates of average supine diastolic pressure, and of the extent of hypertensive vascular disease in heart, kidney and brain. In this term (Table 1) a patient with diastolic pressures averaging more than 140 mm. Hg and grade IV heart failure, uremia and grade IV retinopathy plus encephalopathy would be graded 16 and improvement in any category would reduce the grade. The aim in using the index is to avoid the fallacy of basing

* See Addendum.

conclusions wholly on arterial pressure, while also avoiding the need for cumbersome exposition of concurrent changes in physical status.

Treatment was begun in hospital, usually after two weekly diastolic pressure averages had remained unchanged, and was preceded by use of placebos. Total hospitalization varied from five weeks to six months; before discharge the patient or a relative was taught auscultatory sphygmomanometry so that hospital schedules of observation and record could be maintained at home; however, patients on a four-hour dose schedule were told to omit the early morning dose. Re-evaluation was done in hospital at intervals of about six months, or earlier for treatment of complications.

Such a regimen is practical and necessary only in patients whose disease compels their compliance with a restricted existence and who are also intelligent enough to follow an onerous schedule of self-medication. The groups studied are therefore relatively small. On the other hand, the severity of their disease was such that the changes observed seem the more indisputably the results of treatment.

Hexamethonium was given orally or parenterally. Initial intramuscular or subcutaneous dose was that found to be hypotensive on intravenous test injection; initial oral dose was 125 mg. every four hours. Blood pressures were measured, supine and standing, before each dose which was then regulated according to the standing systolic pressure with the aim of avoiding severe orthostatic hypotension. A few patients were given oral pendiomid® (N,N,N′,-N′-3-pentamethyl-N,N′-diethyl-3-azapentylene-1,5-diammonium dibromide) and the effects of this drug were considered together with the like effects of hexamethonium.

TABLE I
COMPOSITION OF THE SEVERITY INDEX*

Datum	Units Assigned				
	0	1	2	3	4
1. Diastolic pressure, average	95 or	96–110	111–125	126–140	140
2. Cardiac (American Heart Association classification)	0	I	II	III	IV
3. Renal					
Proteinuria, gm./24 hr.	0.2 or	0.2–0.5	0.51–1.0	1.1–3.0	3.0
Serum creatinine, mg./100 ml.				1.5–3.0	3.1
4. Cerebral fundi (Keith-Wagener)	0	I	II	III	IV
Signs	0	0	Severe headache	Old stroke	Encephalopathy or fresh stroke

* Points assigned under each of four panels in grading severity of disease. Each panel is given a value, ranging from 0 to 4, and their sum forms the composite index. Where a panel is graded by two components, the sum of the estimated units is divided by two to establish the value for that panel.

RESULTS

1. Ganglion-blocking Agents Alone. The initial hypotensive treatment in the twenty-three patients was parenteral hexamethonium in eighteen, oral hexamethonium in two and oral pendiomid in three; most of the eighteen were subsequently observed during oral administration of one or other ganglion blocker.

The route of medication was chosen partly from the estimated severity and progress of the patient's disease, having in mind the more rapid and predictable effect of parenteral than oral hexamethonium. Hence, of the eighteen initially treated parenterally seventeen were considered malignant and only one diagnosed as severe essential hypertension; the mean severity index of the seventeen was 11.3 (range 8.0 to 14.5). Of the five given the drugs orally at the outset of treatment four were considered as severe essential and one malignant hypertension; their mean severity index was 7.5 (range 5.5 to 8.0).

A. Parenteral hexamethonium: The sequence of events in the seventeen patients with malignant hypertension is summarized in Figure 1 in terms of total severity index and of values assigned the blood pressure panel. The data given

are means, subgrouped according to survival. Only one patient showed little effect of treatment on total index or blood pressure and died of the disease within two months. The others found some relief which was usually temporary; in two patients it persisted for more than one year. did not benefit from tolerated doses and two, whose physical status improved, have continued treatment for more than six months. One patient, who showed some initial response, discontinued medication and died some months later of myocardial infarction.

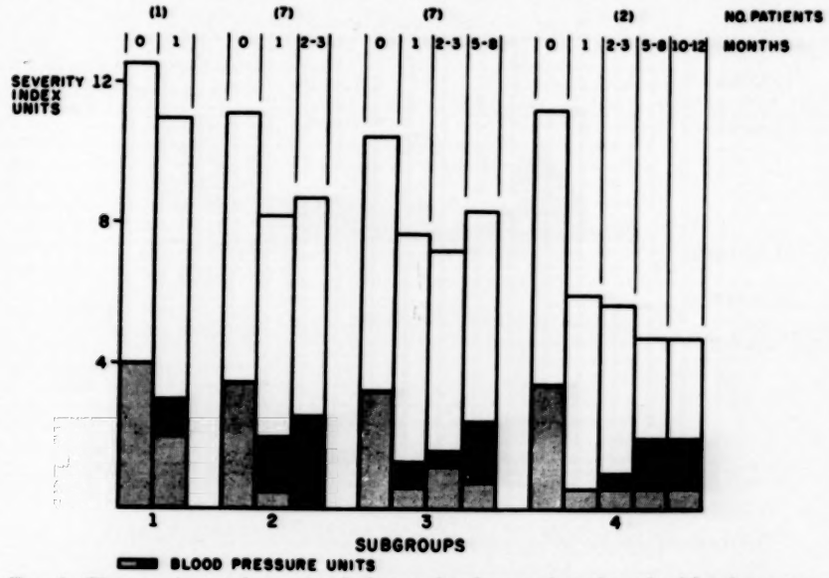

FIG. 1. Changes in total severity index and values assigned to the blood pressure panel in severity units observed in seventeen patients with malignant hypertension prior to (0 months) and during succeeding months of treatment with hexamethonium parenterally. The patients are distributed in four subgroups by approximate length of survival on treatment. The single cross-hatching below indicates average supine diastolic pressure severity value and the double cross-hatching the decrease in diastolic pressure on standing.

The initial severity of the disease was roughly equal in each subgroup and did not determine survival. Rather, the degree and duration of relief were functions of extent and persistence of control of supine diastolic pressure. In contrast, persistence of orthostatic hypotension was not a criterion of a favorable outcome. Figure 2A shows the progress of a patient whose unfavorable course was associated with increasing supine diastolic pressures, while orthostatic hypotension persisted; the more favorable course shown in Figure 2B is that of a patient whose supine and orthostatic depressor responses to treatment were maintained over many months.

The one patient with essential hypertension whose initial treatment was parenterally administered is not included in the composition of Figure 1. During two years' treatment her index of supine pressure has risen from 1.0 at one month to 3.0, but without recurrence of proteinuria or increased cardiac enlargement.

B. Oral administration: Among the five patients whose initial treatment was given orally, two

C. Mortality: At this time, two of the seventeen parenterally treated patients with malignant hypertension survive. Pulmonary disease was the cause of death in seven; of these, five showed pulmonary fibrosis at autopsy; two, not examined post mortem, had radiographic changes construed as multiple pulmonary infarcts although the association of these signs with orthostatic dyspnea suggests that the lesions may have been those of pulmonary fibrosis. Cardiac and renal failure due to advancing vascular disease was the cause of death in five. Two deaths occurred in patients whose courses had been considered favorable; one died at sixteen months, presumably from rupture of a widely dilated aorta and the other at ten months of a cerebral accident. One patient, who had never been satisfactorily controlled, died at four months, suddenly, from an unknown cause.

2. Hexamethonium and Hydralazine. One rationale in combining these drugs is that hexamethonium acts by suppressing a neural and hydralazine another factor which is believed to

be renal. Since there is no useful *a priori* means of testing the concept, it can only be supported *post hoc* by showing that combined treatment is commonly much more effective than treatment with either drug alone. A more empirical reason for combined use of the drugs is that hexamethonium may suppress the side-effects caused by hydralazine.[6,9,10]

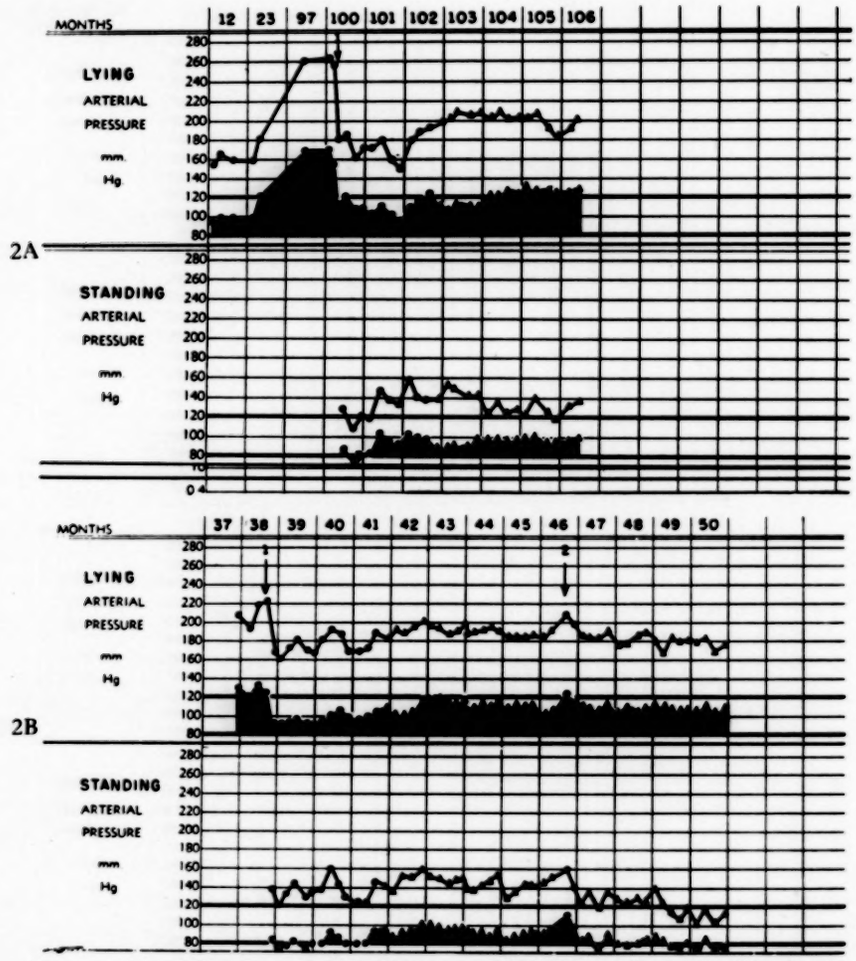
MONTHS
12 23 97 100 101 102 103 104 105 106
LYING ARTERIAL PRESSURE mm Hg
STANDING ARTERIAL PRESSURE mm Hg
2A
MONTHS
37 38 39 40 41 42 43 44 45 46 47 48 49 50
LYING ARTERIAL PRESSURE mm Hg
STANDING ARTERIAL PRESSURE mm Hg
2B

FIG. 2. A, graphic representation of the course of supine and standing blood pressures in a patient whose treatment with parenteral hexamethonium was begun at the time indicated by arrow 1. In this and similar charts months indicate known duration of hypertension; blood pressures are charted as open circles (casual pressures), closed circles are weekly averages of blood pressure in hospital and triangles averages of home pressures. B, courses of supine and standing blood pressures in a patient whose treatment with parenteral hexamethonium was begun at arrow 1 and replaced by oral pendiomid at arrow 2.

The study was done in fourteen patients, nine with malignant and five with severe essential hypertension. Among the nine, four showed signs of advanced nephrosclerosis and one suffered from chronic pyelonephritis.

The initial treatment in six patients consisted of the two drugs in combination; five of these were given hexamethonium orally and one parenterally. The first hypotensive medication in the other eight was hydralazine; hexamethonium was added when it was apparent that they had not responded satisfactorily to hydralazine alone. Patients from both these subgroups were subsequently observed over periods of several weeks during treatment with one or other agent alone, often in alternation. The periods of observation in individual patients extended from ten weeks to three years. The detailed schedules of treatment and response are listed in Table II.

A. Combined initial treatment: Only two of the six patients (No. 2 and 4) showed more effect

from the combination than from either drug alone, and this in the case of No. 4 was limited to increased orthostatic hypotension, which is not a material gain. Hexamethonium accounted for the whole of the favorable responses in two (No. 1 and 3) and hydralazine in one (No. 6) while one patient (No. 5) was resistant to both drugs alone and in combination.

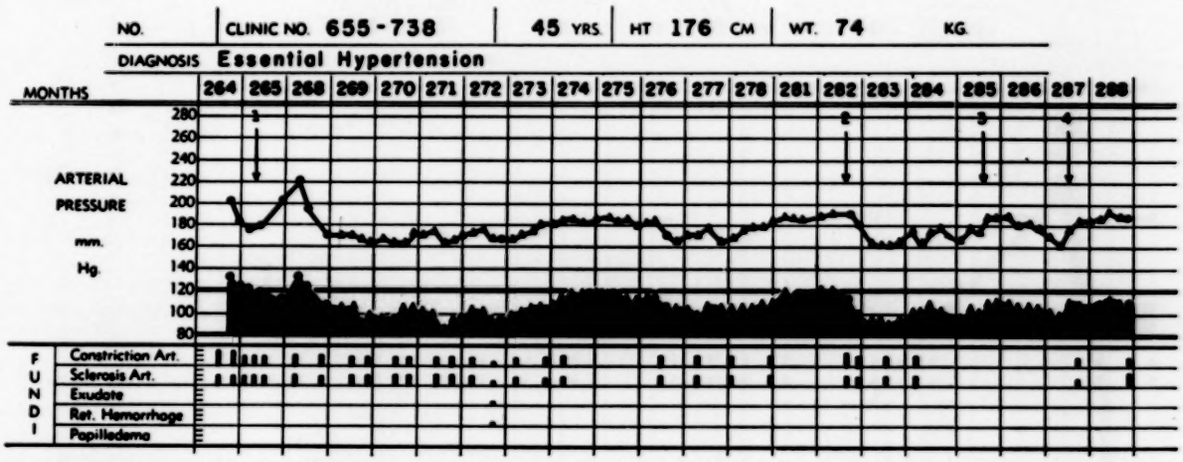

FIG. 3. Blood pressure and fundus changes in patient No. 12. Arrow indicates the start of hydralazine treatment, arrow 2 the beginning of combined hydralazine-hexamethonium treatment, arrow 3 treatment with hexamethonium alone and arrow 4 combined treatment again.

B. Initial hydralazine, subsequent combined: Among these eight patients three (No. 7, 8 and 13) showed some greater effect from combined than from single drug treatment. Two others (No. 11 and 14) may have shown some gain but their courses are complicated. Thus No. 14 showed some response to hydralazine alone, which she maintained equally during treatment with hexamethonium; neither response was satisfactory, so that she was given a course of bacterial pyrogen which lasted three weeks and was complicated by the onset of angina pectoris; at the end of this time hexamethonium was somewhat more depressor than before pyrogen treatment and hydralazine had some additive effect. The possible gain in No. 11 arose presumably from the specific effects of hexamethonium on congestive heart failure, rather than the hypotensive action. Two patients (No. 9 and 10) gave some response to hexamethonium but has no gain from hydralazine. The course of one patient (No. 12) is shown in Figure 3 because it illustrates spontaneous fluctuations of pressure and the fact that none of the regimen resulted in distinct benefit.

C. Mortality: Of the fourteen, seven survived. Mortality is less than in those first treated with parenteral hexamethonium alone because the initial severity of the disease was less (index 7.6 rather than 11.3). Three died during the period of the study. Two were under combined treatment at the time; one died of coronary insufficiency and the other of renal failure and "pneumonia" which may have been pulmonary fibrosis. One was receiving hydralazine alone and died in vascular collapse after a brief, afebrile course of pericarditis and pleuritis; he did not show the electrophoretic or serologic findings of the rheumatic and febrile syndrome. Four died after the period of study, three primarily of renal failure and one of presumed dissecting aneurysm. Four of the seven survivors continued to receive the combination.

D. Value of combined therapy: The observations do not show that combined treatment is commonly much more effective than treatment with either agent alone. Only two (No. 2 and 8) of fourteen patients gained from the combination in a decrease of average supine diastolic pressure greater than 10 mm. Hg. The regimen may have empirical value in temporarily securing prompt control of severe hypertension with hexamethonium while increasing hydralazine dose to a level which it is hoped will be effective in maintenance. The hope of obtaining sustaining additive effects may be an indication in some cases. However, the additive effects are usually small; there is no evidence of synergism, no significant protection against the disagreeable side-effects of hydralazine to which the side-effects of hexamethonium are commonly added.

Problems and Perils. The problems created

TABLE II*

COMBINED THERAPY

Patient No.	Severity Index Units						Hydralazine Dosage (mg./day)	Ganglion Blocker (gm./day)	Duration (wk.)
	Blood Pressure		Cardiac	Renal	Cerebral	Total			
	Lying	Standing							
1	(136)3	.....	2	4	2	11	0	0	5
	(109)1	76	2	3.5	2	8.5	800	.05–.1†	8
	(120)2	.....	2	3.5	2	9.5	800	0	2
	(102)1	66	2	2.5	2	7.5	0	.05–.1†	26
2	(132)3	....	1	0.5	2	6.5	0	0	2
	(121)2	(100)	1	0.5	2	5.5	750	2.5	12
	(100)2	(103)	1	0.5	1	4.5	750	2.5	18
	(148)4	(114)	1	0	1	6.0	0	2.5	4
	(121)2	(101)	1	0	1	4.0	500	2.5	26
	(120)2	(105)	1	0	1	4.0	500	.....	8
3	(128)3	.....	1	0.5	1.5	6.0	0	0	2
	(100)1	(84)	1	0.5	1.5	4.0	750	2.5–3.0	28
	(108)1	(106)	1	0	1.0	3.0	0	3.0–3.5	10
	(109)1	(103)	1	0	1.0	3.0	....	3.0–3.5	26
	(118)2	.....	1	0	1.0	4.0	800	0	6
4	(127)3	.....	2	4	2	11.0	0	0	2
	(123)2	(93)	2	3.5	2.0	9.5	900	2.0–3.0	4
	(128)3	(111)	2	3.5	1.5	10.0	900	6	8
	(130)3	(113)	2	3.5	1.0	9.5	750	5	40
	(140)3	(126)	2	3.5	1.0	9.5	0	5.6	12
5	(120)2	.....	2	0	2.5	6.5	0	0	3
	(116)2	(107)	2	0	2.5	6.5	750	1.5–3.0	5
	(125)2	(104)	2	0	2.5	6.5	0	3.0–5.0	5
6	(109)1	.....	3	0	1	5.0	0	0	3
	(92)0	(80)	2	0	1	3.0	900	2.0–3.0	4
	(85)0	.....	2	0	1	3.0	900	0	2
	(82)0	.....	2	0	1	3.0	300	0	40
7	(140)3	.....	1	0	2	6.0	0	0	2
	(128)3	.....	1	0.5	2	6.5	800	0	9
	(115)2	(105)	1	0.5	2	5.5	800	0.2†	4
	(109)1	(98)	1	0.5	1.5	4.0	800	0.2†	12
	(110)1	(104)	1	0.5	1.0	3.5	800	0.2†	20
	(118)2	(115)	1	0.5	1.0	4.5	0	0.2–0.3†	10
	(109)1	(108)	1	0.5	1.0	3.5	400	0.3†	28
8	(143)4	(136)	3	1.0	1.5	9.5	0	0	12
	(124)2	.....	3	3.5	1.5	10.0	800	0	40
	(109)1	(80)	2	3.0	1.0	7.0	800	0.4	4
	(126)3	(79)	2	3.5	1.0	9.5	600	0.75	40
	(123)2	(83)	2	3.0	1.0	8.0	600	0.75	26
	(132)3	(111)	2	3.0	1.0	9.0	300	0.75	6
	(122)2	(104)	2	3.5	1.0	8.5	600	0.75	18
9	(158)3	.....	1	0.5	1.0	5.5	0	0	2
	(130)3	.....	1	0.5	1.0	5.5	500	0	12
	(143)4	.....	1	0.5	3.0	8.5	0	0	4
	(116)2	(90)	1	0.5	2.5	6.0	0	0.45†	4
	(111)2	(83)	1	0.5	2.5	6.0	800	0.45†	4
10	(131)3	.....	0	4.0	2.0	9.0	0	0	3
	(120)2	.....	0	4.0	2.0	8.0	1000	0	4
	(107)1	(84)	0	4.0	2.0	7.0	1000	0.25†	8
	(124)2	.....	0	4.0	2.0	8.0	1000	0	2
	(109)1	(84)	0	4.0	2.0	7.0	0	0.25†	3
11	(120)2	.....	3	4.0	1.0	10.0	0	0	3
	(115)2	.....	3	4.0	1.0	10.0	800	0	12

TABLE II* (*Continued*)

Patient No.	Severity Index Units: Blood Pressure Lying	Blood Pressure Standing	Cardiac	Renal	Cerebral	Total	Hydralazine Dosage (mg./day)	Ganglion Blocker (gm./day)	Duration (wk.)
	(100)1	(98)	3	3.5	1.0	8.5	800	3.0	32
	(112)2	.....	3	4.0	1.0	10.0	800	0	22
	(115)2	(111)	3	3.5	1.0	9.5	800	3.0–3.5	22
12	(121)2	.....	3	0	1.0	6.0	0	0	
	(108)1	.....	2	0	1.0	4.0	1000	0	46
	(116)2	.....	2	0	1.0	5.0	1000	0	26
	(106)1	.....	2	0	1.0	4.0	1000	2.0–2.5	14
	(108)1	.....	2	0	1.0	4.0	1000	2.0–2.5	10
	(109)1	.....	2	0	1.0	4.0	750	2.0–2.5	6
13	(124)2	.....	1	1	2	6.0	0	0	2
	(120)2	.....	1	2	2	7.0	800	0	4
	(108)1	(97)	1	1.5	2	5.5	800	6.0–8.0^{P}	6
	(113)2	(95)	1	1.5	1.5	6.0	0	16.0^{P}	4
14	(132)3	.....	1	0	3.0	7.0	0	0	4
	(118)2	.....	1	0	1.5	4.5	800	0	6
	(122)2	(85)	1	0	1.5	4.5	0	0.3†	9
	.....	.....	..	...	...	....	Pyrogen		3
	(112)2	(90)	2	0	1.5	5.5	0	0.3†	4
	(104)1	(84)	2	1.0	1.0	5.0	800	0.3†	10

* Summary of observations with combined and alternating hydralazine and ganglion blocker. Blood pressures in brackets are means of diastolic pressure during the periods of treatment; numerals not in brackets indicate units in severity index from supine diastolic averages. Severity index units are listed in the cardiac, renal and cerebrovascular panels, sum of the units from each panel listed as total severity index. Dosages are rounded averages during each treatment period; dosages of ganglion blocker indicated by a dagger consist of parenteral hexamethonium and those indicated by the superscript P are pendiomid.

by the use of hexamethonium are familiar and need only be noted briefly. In two patients exercise hypotension developed; in one it was disabling and was not associated with orthostatic hypotension. Practical details of management consist mainly in keeping the bowels and bladder in function, the former with laxatives and the latter with oral or sublingual urecholine®. Prostigmine® or urecholine hypodermically twenty minutes before enemas facilitates expulsion. Pilocarpine eyedrops relieve uncomfortable pupillary dilatation. In this connection, intravenous injections of hexamethonium were found to decrease pupillary size and intraocular tension in two patients with glaucoma controlled with eserine; this effect may be due to potentiation by ganglion blockade of the peripherally acting agent. This experience is noted because glaucoma had been suggested as a contraindication to use of hexamethonium.

These aspects of ganglion blockade sometimes become distinct hazards. Thus gastric atony in one patient was so severe that treatment was continued only after gastroenterostomy; in two patients paralytic ileus developed, in one with fluid levels by x-ray, which was relieved by gastric suction and repeated dosage with prostigmine. Earlier recognition and control of incipient gastrointestinal paresis might have prevented ileus. Two patients are presumed to have died of myocardial infarction consequent on orthostatic hypotension and one sustained a myocardial infarct.

Dangerous supine hypotension was seen after initial doses in two patients, one of whom was given only three mg. Both became temporarily oliguric and azotemic; hypotension was controlled with noradrenaline in one. A few patients in renal failure have shown prolonged depressor responses, apparently the result of decreased excretion. Maximum hypotension was

sometimes delayed one or two hours after intravenous injections of test doses; the mechanism of this response is not known.

The pulmonary fibrosis found in five patients at postmortem examination, and which may have been a cause of death in three others, is an unfortunate complication of the use of hexamethonium in severe hypertensive disease.[11] Its mechanism is unknown. It is probably a specific aspect of the unphysiologic situation created by prolonged partial autonomic block.

Emergency Uses. The use of hexamethonium in the emergency management of congestive heart failure is well recognized[12] but was not a problem in our patients. It was used to control hypertensive encephalopathy in ten; these presented headache, vomiting, restlessness and confusion; three were in semicoma or coma. The intravenous dose was that amount which would decrease diastolic pressure to about 100 mm. Hg; this level was maintained by subsequent intramuscular doses. In two, doses of 200 mg. hexamethonium intravenously were ineffective; these were treated by infusions of sodium nitroprusside. The others responded to doses of 30 to 100 mg.; those not in coma or semicoma were subjectively relieved within the hour while the others required some forty-eight hours of sustained normotension for recovery.

In principle, hexamethonium hypotension should be beneficial in cerebral hemorrhage, especially in subarachnoid bleeding, but injurious in cerebral thrombosis. The drug was given to several patients who were presumed to suffer from cerebral hemorrhage. Massive intracerebral bleeding was present in four who died and who soon lost whatever depressor responsiveness they may have first shown to the drug. The nature of the lesion is unknown in those who recovered; these responded to repeated injections by sustained decreases in blood pressure. The observations suggest that hexamethonium may favorably influence the course of cerebral hemorrhage and that the cause is in any case lost in those who rapidly become resistant to the drug.

Comments. The experience shows that hexamethonium is a valuable agent in the control of severe hypertension. Tolerance limits the duration of its effectiveness in many patients, side-effects can usually be controlled. It is perhaps most useful in the initial treatment of those who will later respond to hydralazine, and this seems the best argument for initial combined therapy. Its disadvantages are numerous and well known. They impose large restrictions and demands on the patient, particularly during home care.

The experience does not sharply delimit any patient group whose sustained responsiveness to the agent would suggest that nerve impulses blocked by hexamethonium were primary mechanisms in their hypertension. The deaths of two patients who had responded for long periods were apparently due to irreparable consequences of their former malignant hypertension; these illustrate the importance of early control of this dangerous condition.

Reserpine. The properties and uses of alkaloid of Rauwolfia serpentina were topics of a recent conference[13] during which our preliminary data were described. Its action is primarily central. The drug was used as the sole antipressor agent in thirteen patients, of whom five showed definite antipressor effects. Responsiveness was not determined by severity of the disease or the capacity to respond to hydralazine. Reserpine was used in association with hydralazine in eleven patients, and in five gave an added effect. Six patients were tested during treatment with hexamethonium; two showed an added hypotensive effect and two improvement in constipation. The doses used in this group ranged from 0.5 to 10 mg. daily. As the experience with the drug has been extended it seems likely that average maintenance dosage in patients who respond will be less than 0.5 mg. daily. The most common and troublesome side effect is nasal stuffiness which does not respond to antihistaminics but tends to abate with time; three patients have been troubled by a hacking cough. Langour is common and persistent. Therapeutic responses to the drug usually appear during the first three weeks of treatment and are unequivocal. The drug is a useful and potent agent in some patients with severe as well as mild hypertension. Present experience suggests that it may be a desirable initial trial medication in patients whose disease is not rapidly advancing. (Fig. 4.)

Diet in Hypertension. Strict sodium restriction (about 200 mg. Na daily) is therapeutically antipressor in a minority of patients.[14] In the absence of azotemia and renal failure, the severe protein restriction imposed by the rice diet seems unnecessary. Palatable low-sodium food and recipes make the regimen less onerous than it was. However, few patients tolerate its restrictions and many find them impossible in daily life. Further, as Watkin, Froeb, Hatch and

Gutman[15] have pointed out, the critical level of sodium intake is extremely low in patients with severe hypertension and little more sodium than is allowed causes return of hypertension. We have not been able to predict in advance who will respond to sodium restriction. All in all, low-sodium dietotherapy is a desirable form of treatment in a disappointingly small proportion of patients, although probably more advantageous than hexamethonium or hydralazine in those who tolerate and respond to the regimen.

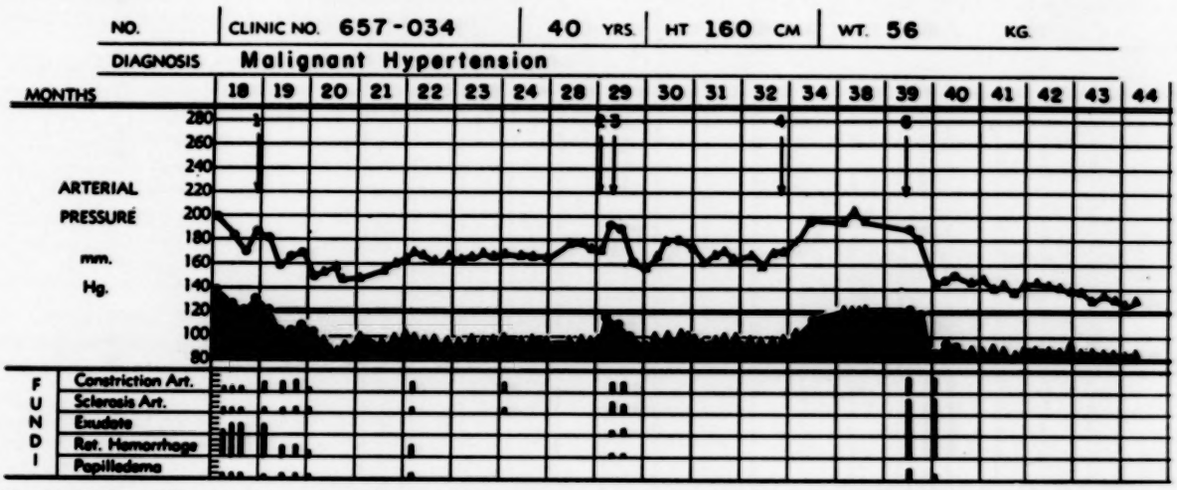

FIG. 4. Course of blood pressure and fundus changes in a woman treated first with hydralazine (arrow 1), whose blood pressure rose when hydralazine was discontinued (arrow 2) and fell again when treatment was re-instituted (arrow 3); hydralazine was again discontinued (arrow 4) because of the development of the rheumatic and febrile syndrome; reserpine was begun at arrow 6.

Sympathectomy. The experience of seventeen years has not greatly altered original estimates of the effectiveness of these operations.[16] A small proportion of patients responds dramatically to lumbodorsal sympathectomy; a larger proportion obtains modest relief and approximately one-third receive no measurable benefit. If there were certain means of predicting which patients would respond satisfactorily to the operation, it would be the procedure of choice in them as compared to the costs and other disadvantages of hydralazine or hexamethonium. Until this can be accomplished, sympathectomy is indicated in patients with advancing vascular disease, primarily cardiac, who do not respond to sodium restriction and in whom treatment with hydralazine or hexamethonium is impractical.

SUMMARY

1. The pharmacotherapy and management of severe hypertensive disease are reviewed primarily with regard to hydralazine and hexamethonium. The former gives sustained relief and decreases mortality in about half of the patients treated; its use is complicated by common, usually transitory side-effects and, in some patients, by a delayed toxic response characterized as a rheumatic and febrile syndrome.

2. Experience with the use of hexamethonium alone shows that it gave temporary relief in sixteen of seventeen patients with malignant hypertension; the duration of relief was limited by tolerance to its depressor effect on supine diastolic pressure. Benefit was not determined by persistence of orthostatic hypotension.

3. Some additive effects of combined treatment with hexamethonium and hydralazine were defined in seven of fourteen patients tested with these drugs separately and in combination. However, only two gained more than ten mm. Hg decrease in average supine diastolic pressure from the combination. Side-effects of hydralazine were not mitigated by effective doses of hexamethonium.

4. Preliminary observations indicate that reserpine (serpasil®) is a potent antipressor in some patients when used alone or in association with other drugs.

5. In perspective, the considerable efficacy of specific agents and procedures in some patients, but not in others, suggests that hypertension in these is sustained by different, definable mechanisms. Insight into these should diminish the large measure of poorly rationalized empiricism which presently clouds the treatment of hypertensive disease.

Addendum. The following tabulation represents serial observations of renal function in the patient (Clin. No. 645 907) who developed hydralazine syndrome with gross renal impairment:

Date	C_{PAH} (ml./min.)	C_M (ml./min.)	F.F.	T.P. (gm./100 ml.)	Alb. (gm./100 ml.)	Hem.	B. Pm. (mm. Hg)	Ur.P. (gm./24 hr.)
9/51	319	93	0.29	7.2	4.3	0.54	199	0.2
	*438	81	0.19				190	
6/52	371	77	0.21	8.2	3.7	0.48	112	0.1
3/54	92	4.6	0.05	7.1	2.5	0.24	125	1.8

Hydralazine treatment from October, 1951; the data which follow the asterisk represent effects of an intravenous test dose (0.3 mg. per kg.). Data listed are plasma clearances (low concentration) of p-aminohippurate and mannitol (latter times 1.1) per 1.73 sq. m. per min., filtration fraction, serum total protein and albumin in gm. per 100 ml., hematocrit index, means of arterial pressure (systolic + diastolic/2) and urine total protein. The microscopic renal lesions are those of healing malignant nephrosclerosis, and, while some of the glomerular capillary changes are consistent with the diagnosis of systemic lupus erythematosus with renal involvement, these can be adequately explained as sequelae of the presenting major disease.

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Conference on Therapy

A Re-evaluation of Quinidine Therapy

THESE are stenographic reports, which have been edited, of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. GEORGE READER: We have had a few conferences on quinidine in recent years but the subject seems to be practically inexhaustible. There always remain questions of uses and abuses, indications and contraindications which are in need of further elaboration. Such a discussion is of particular importance at the present time in view of the growing interest in substitutes for quinidine. Dr. Gold will start off the discussion.

DR. HARRY GOLD: The subject of quinidine therapy is one which can carry itself along satisfactorily in a conference through the medium of questions and answers. I will make a few introductory remarks on the subject for the purpose of getting the discussion under way. Quinidine has had a stormy career. When it was first introduced for the treatment of auricular fibrillation about thirty years ago, it was enthusiastically thought to end the problems of treating auricular fibrillation. There were items in the newspapers to that effect. As you know, that did not turn out to be the case. The situation not only changed but also reversed itself, and it was not very long before large numbers of observers came to regard quinidine as a dangerous therapeutic agent, some preferring to avoid it. Experience over the years has helped to define more satisfactorily the place of quinidine in therapy of the heart. It is now possible to put into effect a plan of treatment which insures the maximum benefit from the drug with the minimum of risk, often a negligible risk. By far the majority of patients with premature contractions that are troublesome, paroxysms of auricular fibrillation or flutter, paroxysms of auricular or ventricular tachycardia, can count upon satisfactory control on a suitable system of quinidine medication. It is a noteworthy feature of the literature on the efficacy of quinidine that the incidence of satisfactory results differs widely from one observer to another. I believe this is largely a matter of dosage. Dosage is probably the weakest spot in the whole system of quinidine therapy. I should like to make a few remarks about dosage.

Quinidine is a drug which almost invariably produces minor toxic effects before it produces serious effects. In this respect it is much like digitalis and therefore the only proper system of dosage is one in which an appropriate concentration in the body is built up gradually by the cumulation of fractions. The purpose is twofold. On the one hand it avoids serious toxicity; on the other, it eliminates fixed upper limits of dosage which greatly restricts the usefulness of quinidine in the more tolerant cases. One sees it stated that if a daily dose of 2 or 3 gm., or something of the sort, fails to produce the therapeutic results, the drug should be discontinued. Such procedure is no more applicable to quinidine therapy than to digitalis therapy. Each individual patient should be treated by gradually increasing dosage, watching more closely at the higher level of dosage for minor toxic effects which call for cessation of the drug. By this means one is certain to include the more resistant cases in therapeutic successes and to avoid serious toxicity.

I might say at this point that the place of quinidine in heart disease relates only to the control of abnormal rhythms. It has nothing to do with the problem of heart failure except insofar as heart failure may be involved indirectly. A person sixty-five years of age with arteriosclerotic heart disease sometimes goes into congestive failure when he develops an attack of auricular fibrillation. Quinidine may prevent the paroxysm, and in that way prevent the congestive failure, but the direct action of the drug relates only to the matter of controlling ectopic rhythms. Quinidine may be regarded as a "broad spectrum" drug in relation to disorders of rhythm. It favorably affects all the ectopic

disorders of rhythm: premature contractions, auricular tachycardia, ventricular tachycardia, auricular fibrillation, auricular flutter. The only situation in which it has no place is heart block with Adams-Stokes attacks.

As patients present themselves with abnormal rhythms, two distinct problems emerge. The patient may be seen during such an attack. Or he may consult his doctor because he has been having attacks although his rhythm is normal at this time. Here, then, are the two problems; one, to abolish a current attack, the other to prevent recurrences. They should be kept separate in our minds because the treatment for the two is different. The treatment of the paroxysm of abnormal rhythm is essentially a bed problem. The patient ought to be at complete rest and under very close supervision. The course of treatment should be a matter of a few days, not one of weeks as a rule. The prevention of paroxysms is essentially an ambulant problem. I doubt that it is wise to treat it as a bed problem, for a system of dosage which proves effective in preventing attacks while the patient is at complete rest may prove to be quite inadequate when the patient is up and about and exposed to physical and emotional stress. Perhaps this is enough by way of preliminary remarks.

DR. READER: Are there any questions?

DR. WALTER MODELL: I think it is reasonable to assume that Dr. Gold is going to say more about this subject. It is just a matter of asking the proper questions. Might we have a word about this item in dosage. It is customary to use a small test dose in treatment with quinidine. I have a notion that it has limited value. What about that?

DR. GOLD: I agree. Do you think it has any value?

DR. MODELL: I don't think it is of any value at all because I do not think it discloses the idiosyncrasies that may develop with the other doses. Have you ever seen a very small test dose bring out the reactions of idiosyncrasy?

DR. GOLD: No. From a review of the literature which we made some years ago we decided that no one ever discovered a reaction from the 3 gr. test dose which altered the course of treatment.

DR. SEYMOUR H. RINZLER: Does the dosage of quinidine depend upon the type of arrhythmia? Are the doses larger or smaller for the more or less serious forms of arrhythmia?

DR. GOLD: I don't believe so. There are patients with premature contractions, which are relatively harmless extra beats, who may be very sensitive or exceedingly resistant to quinidine. The same is true of the more serious form of ectopic rhythm, ventricular tachycardia. Some patients with ventricular tachycardia are very sensitive and others exceedingly resistant to quinidine. The best technic for answering this question as to whether, for example, ventricular tachycardia requires more or less quinidine than, let us say, premature contractions, has never been applied to the subject but I believe that if there is a difference it is not a conspicuous one.

If we look at your question, however, in terms of the gravity of the problem in a particular patient, then we should say that the more severe the paroxysm, the larger the doses and the more intensive the treatment regimen. Consider a particular person, sixty-five years of age, who complains of troublesome premature contractions which give rise to a lump in the throat and some nervousness. At another time this same person may present himself with something else, a paroxysm of auricular fibrillation which has caused marked shortness of breath and edema of the lung. These two situations call for different schedules. In the more serious situation, one starts with larger doses, shorter intervals, and is involved in somewhat greater risks of toxicity. In the less urgent situation of premature contractions, one may start with smaller doses, longer intervals, and take one's time eliminating the risk in the endeavor to bring them under control.

DR. MODELL: In building up this concentration, Dr. Gold, how do you proceed in relation to the shortening of intervals and increase in the size of the individual fractions? What minor toxic symptoms do you look for as indications for interruption of the drug?

DR. GOLD: Let us consider first paroxysms of an ectopic rhythm such as paroxysms of auricular tachycardia, a situation in which the problem is that of prevention. What I usually do in such a case is to start with 0.3 gm. quinidine sulfate by mouth three times a day. I tell the patient to take this dosage until there is another attack. If another attack does not occur, he continues that dosage indefinitely. After another paroxysm he is instructed to take two tablets, 0.6 gm., three times a day. He continues this in the same manner until there is another attack. This calls for an increase in dose and is accomplished by shortening the interval to every four hours instead of every six hours. It is the appearance of

another attack which reveals the need for higher concentrations. I think it is wise to warn the patient that it may take a few months to work out that level of dosage which will ultimately keep him free of attacks. This avoids discouragement. When a daily dosage level around 3 gm. is reached, it is well to check with the electrocardiogram, made after the total dose for that day, for prolongation of the QRS time. It begins going up at about that level and sometimes reaches values 50 per cent or more above the normal. In some patients doses as high as 6 gm. a day are tolerated without this effect but in others the spreading of the QRS time occurs fairly early. If there has been no change, one can increase the dose by another gram or so a day if there is need for it, again checking with the electrocardiogram daily for evidence that a QRS time of, let us say, 0.08 second has gone up to 0.12 or thereabouts.

DR. READER: Suppose you find the QRS time has gone up to 0.12 second, do you have to discontinue the quinidine? Will not the depression of intraventricular conduction continue to progress as the doses are continued?

DR. GOLD: The curve of quinidine cumulation with the fixed daily dose tends to level off in three to five days so that any effect which is in evidence about five days after a particular daily dosage level has been taken is not likely to increase if the same dose is continued for long periods of time.

DR. READER: That the QRS time should behave in this manner is fascinating, although it is not clear to me as to what keeps it from going further as the doses are continued.

DR. GOLD: There is nothing really remarkable about this story of quinidine dosage and cumulation, for it applies to other drugs that have been so tested using either chemical determination of concentrations or biological measures of intensity of action. The rule is that cumulation is a self-limiting process when a fixed daily dose is being taken. If one gives a gram of sodium bromide daily and measures the bromide level in the blood, it may be noted that the concentration begins going up day after day and then reaches a level which is not exceeded even though the same daily dose is continued. If one gives 0.2 gm. of digitalis daily to a patient with auricular fibrillation and a rate of 140, and follows the heart rate changes in the ensuing days and weeks, it may be noted that the rate begins to decline gradually day after day and then reaches a level of perhaps 100, below which it will not go although the same daily dose is continued. Clearly, in terms of effect, there was cumulation at the beginning which was no longer in evidence after the level effect was reached. The same is true of quinidine, with the characteristics of the curve of this rapidly excreted drug.

DR. E. HUGH LUCKEY: I have two questions. What contraindications appear in the clinical picture to the administration of quinidine? The second question is a repetition of the one asked by Dr. Modell: what manifestations during cumulation call for discontinuing the drug prior to reaching the therapeutic objective?

DR. GOLD: I am not sure that there are any clear-cut contraindications to the use of quinidine in disorders of cardiac rhythm. There are situations in which the clinical course is not favorably influenced by restoring normal rhythm. This applies especially to patients with chronic auricular fibrillation. Most of these patients do better when they are allowed to fibrillate and their rates are slowed by digitalis. There is the possibility that the restoration of a normal rhythm in auricular fibrillation sometimes leads to the discharge of emboli. One might say therefore that a predisposition to embolization from the auricle, as in mitral stenosis, might constitute a contraindication to the use of quinidine but the evidence on this point is indecisive for there have been records of cases in which the restoration of a normal rhythm in auricular fibrillation led to the cessation of embolization which had been occurring previously.

Now for the next question regarding toxic manifestations of quinidine action which call for cessation of the drug. Impairment of intraventricular conduction as shown by prolongation of the QRS time is one indication for interruption of the drug. We do not know exactly where to place the danger point and we have arbitrarily adopted the position that a prolongation of the QRS time to that of 0.12 second or more, the picture of bundle branch block, should not be allowed to continue. If this occurs before normal rhythm is restored, it is safer to regard this as a therapeutic failure for quinidine. Disturbing deafness and blurred vision call for reduction of the dose. Some patients show inordinate gastrointestinal intolerance with nausea, vomiting and diarrhea. This defeats the therapy, at least by the oral route. Some of these patients may be managed by the parenteral route. It would be well to have a blood platelet count made for signs of thrombocytopenia. In

the mild forms this promptly rights itself when the drug is discontinued, while in the severe forms fatal thrombocytopenic purpura has ensued.

DR. READER: Is there a direct relationship between the size of the dose and the sensitivity of the thrombocytes? A few days ago a fatal case of thrombocytopenic purpura was presented at our clinico-pathologic conference. Attention was called to reports in the literature of similar cases which showed that this reaction may occur very early in the course of treatment, even after the first dose. It does not seem to be a matter of cumulation of the drug.

DR. GOLD: The two cases that I have seen were receiving very large doses, 3 and 4 gm. daily. One was a patient with idiopathic thrombocytopenia. Without quinidine, the blood platelet count was about 96,000, and during quinidine administration it declined to about 30,000 with the appearance of ecchymoses. This was repeated several times. It was deemed unwise to try to control the paroxysms of auricular fibrillation under these conditions and quinidine was discontinued. The other was a fatal case, a physician who found it necessary to take 3 to 4 gm. of quinidine sulfate daily to keep free of paroxysms of auricular fibrillation. After many months on this dosage ecchymoses developed. Within a few days these increased to a generalized purpuric eruption and the patient died in convulsions before anything could be done from what was apparently a cerebral hemorrhage. These two were reactions to large doses and only after prolonged treatment. In the first of these cases I believe we anticipated disaster by finding the marked depression in the number of blood platelets. Had we had more blood counts in the second case it is conceivable that disaster might have been averted there also.

DR. READER: I think this is the kind of idiosyncrasy in which the reaction is apt to occur abruptly at a dose which is similar to the one which had previously been tolerated well, and that dose need not be a large one. It seems to be similar to the situation of thrombocytopenia during the use of hair dyes. It is not a matter of the amount that is used. The reaction appears to come about as the result of some special trigger mechanism. The patient may use the compound for several years without trouble and then suddenly a reaction occurs.

DR. GOLD: I am still wondering whether one is justified in the position that there is no relationship between the dose and the severity of the reaction, for in the majority of allergic reactions, I believe, the severity of the reaction still depends upon whether the level of dosage is low or high.

DR. LUCKEY: I doubt that doing blood platelet counts is of any value in relation to quinidine therapy because the thrombocytopenic reaction appears so quickly. It is a great deal of work, and probably futile.

DR. READER: The point is that when the platelets drop they do so rather precipitously. If the count drops to a level of 60,000, the patient bleeds. One patient may show only a few black and blue marks while in another a cerebral hemorrhage may develop. In almost all recorded cases the platelet count is restored in three or four days after the drug is discontinued.

DR. GOLD: It may well be that in some situations the reaction occurs with such speed and overwhelming force that nothing can save the patient. I believe that the case I have just cited is one in which we may have saved the patient by reason of the detection of a sudden decline of the platelets to 30,000. Might we perhaps say that in any patient in whom a few purpuric spots appear, quinidine should be discontinued at once and a blood platelet count should be made? This might help to discontinue the drug in time and prevent a few more doses from tipping the balance unfavorably.

There is one more toxic manifestation of quinidine which calls for interruption of the treatment. It is the appearance of an idioventricular rhythm or ventricular tachycardia. It is sometimes brought on by quinidine itself but more often by large doses of quinidine in the patient who has been digitalized. It is sometimes confused with the abnormal rhythm that one is treating. The appearance of any unexpected disturbance of rhythm during quinidine medication calls for at least temporary cessation of the drug and an electrocardiogram to ascertain the nature of the disturbance.

DR. LUCKEY: Would you say that the appearance of ventricular premature contractions during quinidine treatment, which did not exist prior to the therapy, calls for interruption of the drug? This phenomenon has caused us a great deal of trouble. I wonder if I could ask Dr. Perrone to review briefly the last thirteen cases of auricular fibrillation in which we tried quinidine. It is a rather dismal story and I think you will be interested in it.

DR. FRANCES S. PERRONE: An attempt was made to restore a normal rhythm in thirteen patients with chronic auricular fibrillation. The usual schedule called for a dose every two hours for five doses, then every four hours around the clock. It also called for an increase in the daily dosage every two or three days.

DR. MODELL: Were these patients digitalized?

DR. PERRONE: The majority were. The majority were in chronic congestive failure. The auricular fibrillation was of long duration.

DR. GOLD: May I ask the purpose of this study? Was it to see how much better things would be if a normal rhythm were restored in a patient with chronic auricular fibrillation?

DR. PERRONE: Yes, how much better from the standpoint of failure and embolization. This is what happened. In six of the cases normal rhythm was restored. One of these patients died, in one a chaotic heart action appeared, in one ventricular tachycardia developed, in one ventricular premature contractions appeared and in one a gastrointestinal disturbance made it necessary to discontinue the drug. The remaining seven cases were successful, but in one of these restoration of the rhythm was complicated by the appearance of ventricular premature contractions and in another by a chaotic heart action.

DR. GOLD: What is the "chaotic heart action"?

DR. LUCKEY: Any grossly irregular rhythm which is due to ventricular beats of multiple foci.

DR. PERRONE: Among this group of thirteen patients in whom attempts were made to restore a normal rhythm, fairly serious complications which prevented further use of the drug developed in eight.

DR. READER: What was the cause of death in the one patient you mentioned?

DR. PERRONE: Sudden death, cause unknown.

DR. READER: One can only speculate that it might have been a cardiac death or death from embolus.

DR. GOLD: How large was the dose in this patient?

DR. PERRONE: All the doses were in the range of 3 to 4 gm. a day.

DR. GOLD: This is a very interesting experience. Quinidine in 3 to 4 gm. daily doses proved effective in restoring sinus rhythm in only about half of your group of patients and in nearly two-thirds of them the drug had to be discontinued because of toxic rhythms. Do you think that this experience might have been different if these had not been digitalized patients?

DR. LUCKEY: It is quite possible. It is of interest in this connection that the one patient who died had required a fairly large maintenance dose, 0.3 mg. digitoxin daily, for many months.

I believe that we miss a great many of the serious disorders of rhythm during the use of quinidine. One of the patients in whom a normal rhythm was restored reported that she had a very restful night and that she was now feeling well. The intern had quite a different story. He had been up with her all evening before and had observed the chaotic heart action with Adams-Stokes attacks, with some uncertainty as to whether she might even survive. It may well be that the experiences reported in the literature as being so benign may be due to the fact that patients are not watched closely enough and some of these ominous events are overlooked.

There is a point which has occurred to me in connection with these abnormal rhythms, that in the period between the time the ectopic focus is suppressed and the sinus rhythm is initiated, an escape mechanism may give rise to all manner of abnormal beats.

DR. GOLD: I think the point is a good one. If you record the electrocardiogram in a patient with a paroxysm of auricular tachycardia before and during carotid sinus pressure, you may often demonstrate the events in the transition between the abnormal and the normal rhythm. In that transition period a wide variety of abnormal beats may be seen, auricular or ventricular premature contractions, and in one case I recorded a fleeting ventricular tachycardia of 270 a minute. It may very well be that some of the cardiac rhythms which occur in the process of restoration of sinus rhythm by means of quinidine may not be the result of the drug at all but due to the natural tendency for pacemakers in the heart to become inordinately busy when the normal sequence of discharges is interrupted.

DR. READER: How about the digitalis problem? Do you usually counsel stopping digitalis when you start quinidine?

DR. GOLD: When you can get along without the two drugs together, try to do so. This is the policy I pursue. I do not know the full extent of the risk. I cannot even prove that there is a risk except from animal experiments. There the evidence is strong. Dr. Modell and I published the results of some experiments in dogs several years ago in which it was found possible to produce a variety of serious disorders of cardiac rhythm, with cardiac arrest, in digitalized

animals by doses of quinidine which have no such effects in the absence of digitalis. There is something about the synergistic actions of these two agents acting at the same time on heart muscle which gives rise to an effect that is not predictable from the action of either alone. How often this occurs in the treatment of human disease no one knows. The consequences seem to me too serious to try to find out, and so I try to avoid it. In some cases with congestive failure it is possible to do so by the use of salt restriction and the mercurials instead of digitalis to control the symptoms of failure. This allows us to proceed with quinidine as freely as seems necessary. A situation like this sometimes arises in connection with ventricular tachycardia with which congestive failure may co-exist. I do not believe that one should feel free to use as much quinidine as is necessary to control the ventricular tachycardia in such a case if full doses of digitalis have been given for control of the failure.

DR. READER: If the patient with auricular fibrillation has a very rapid ventricular rate, would you be inclined to slow it down by means of digitalis first before you attempt restoration of normal rhythm with quinidine?

DR. GOLD: I do not as a rule. If the decision is reached that the particular individual is suitable for an attempt to restore normal rhythm, I proceed with quinidine directly.

DR. MODELL: Is there not a theoretic objection to the use of the two drugs together? Is there not some indication that the actions of the two are antagonistic in relation to the termination of auricular fibrillation?

DR. GOLD: There is some evidence of antagonism of digitalis and quinidine with respect to the circus movement, but the actions of the two drugs are so complex that the final results cannot be safely predicted, and there are reports of groups of patients in whom auricular fibrillation was successfully terminated by quinidine in patients who were under the effects of digitalis. The answer to that question is indecisive.

DR. SEYMOUR H. RINZLER: If gastrointestinal symptoms appear during the use of quinidine orally, is it possible to proceed at that point by some parenteral method with safety?

DR. GOLD: Yes, the preparation of quinidine sulfate in propylene glycol is very satisfactory for intramuscular injection. It comes in ampuls containing 0.2 gm. per cc. An intramuscular injection of 0.2 gm. at intervals of two or three hours deep into the buttocks helps to build up an effective concentration. I am not sure that this might prove to be the method of choice in terminating a paroxysm of ectopic rhythm. It would get around the cases in which trouble arises as a result of gastrointestinal symptoms.

DR. READER: Suppose you have a patient with auricular fibrillation in whom you build up an effective concentration of quinidine and the normal rhythm is restored, do you continue quinidine after that?

DR. GOLD: That depends. The patient's history will sometimes help to decide the matter. If the attacks are exceedingly infrequent, one every two or three years or so, it is more expedient to treat an attack than to attempt prevention by a maintenance system of quinidine. On the other hand, if the attacks come daily or at some other intervals which are fairly short, I am likely to give the patient regular maintenance dosage to prevent recurrences.

DR. READER: Do you use quinidine in the patient with chronic auricular fibrillation?

DR. GOLD: No, I almost never try to convert these to regular sinus rhythm. It is my own experience and that of many others that this group of patients does better when allowed to continue to fibrillate and take a digitalis preparation to keep down the ventricular rate.

DR. LUCKEY: We have spent the whole session on quinidine and I notice that we have not mentioned pronestyl® which in some quarters has now replaced quinidine in disturbances of cardiac rhythm. Would Dr. Gold say a word about that?

DR. GOLD: My experience with it is limited. I have only tried it in patients in whom quinidine did not prove successful. In these pronestyl also failed.

DR. LUCKEY: We have treated a small series of patients with it. The general pattern of its actions is similar to that of quinidine both with respect to the kind of cases, the results and the toxic effects. I see no advantage in it unless it is for the patient who happens to be intolerant to quinidine or has some idiosyncrasy. In general, a 4 gm. dose of pronestyl will do about the same thing that is to be expected from 1 gm. of quinidine.

DR. DANIEL S. LUKAS: I have been thinking about patients with mitral disease during this discussion. We sometimes see such patients with paroxysms of auricular fibrillation tending toward chronic auricular fibrillation. At the beginning it may have been easy to control these attacks but the time has come when the

attacks are more difficult to control. They are associated with severe dyspnea and pulmonary edema. When do you begin quinidine to restore normal rhythm in such a patient?

DR. GOLD: If I understand your question, the answer is to start quinidine as soon as paroxysms of auricular fibrillation develop. This should be done long in advance of the period when the attacks are so severe that they precipitate pulmonary edema.

DR. LUKAS: Suppose the patient has gotten up to very high doses and severe paroxysms of auricular fibrillation still develop? When do you give up?

DR. GOLD: The principle of dosage which we have discussed throughout the conference applies here as well. Do not give up until you have reached a dosage level which prevents the attacks or produces the various toxic effects which have been mentioned earlier as precluding further use of the drug. You may then turn to digitalis in the endeavor to stabilize the auricular fibrillation and reduce the ventricular rate.

DR. LUKAS: Are you disturbed by the fact that the next attack may precipitate a fatal pulmonary edema, which it sometimes does? During the period while you are trying to boost the dose to the effective level the patient may be having attacks and one of these may prove fatal.

DR. GOLD: Yes, that possibility would disturb me very much but I would not know what to do about it.

DR. LUKAS: Would not the use of digitalis in these patients between the attacks insure a slow ventricular rate when an attack comes?

DR. GOLD: Strangely enough, even when these patients are receiving digitalis the paroxysm of auricular fibrillation is still associated with a rapid ventricular rate as a rule. It seems to require much more than the ordinary dosage of digitalis to keep the ventricular rate low under the stress of a paroxysm of auricular fibrillation.

DR. LUKAS: There are some patients in whom a ventricular rate is effectively controlled with digitalis at levels of 60 or so during paroxysms of auricular fibrillation, in consequence of which the attacks of pulmonary edema are prevented.

DR. GOLD: I agree that there are some. I would myself be inclined to try to control the attacks of pulmonary edema during a paroxysm by salt restriction and mercurial diuretics. I would be inclined to build up the dosage of quinidine fairly rapidly to levels of 3 or 4 gm. daily in the endeavor to control the paroxysms. If this proved ineffectual, I would not be averse to having the patient digitalized with the full realization that a risk is incurred in using large doses of quinidine in the presence of full digitalization. The hazard of the treatment is weighed against the hazard of the condition.

DR. MODELL: I would like to point out that the hazards of quinidine in the various disorders of rhythm are not due solely to the toxicity of the drug. Is it not a fact that there is an inherent danger in terminating an abnormal rhythm by whatever drug it is accomplished?

DR. GOLD: You are quite right. Dr. Luckey had earlier called attention to the fact that in the transition between the ectopic and the normal rhythm, escape rhythms may reveal themselves which may be very disturbing. After an ectopic rhythm is blotted out the heart may be left without a pacemaker for a sufficiently long time to cause disastrous effects. This may be the cause of some of the sudden deaths, not necessarily the result of drug toxicity but the result of the removal of the ectopic focus which was at the time apparently the only effective pacemaker.

DR. LUCKEY: In regard to ventricular tachycardia, I think it is well to bear in mind the difference between the two situations, one with and one without concomitant A-V block. If the ventricular tachycardia is the result of an unusually excitable focus in a ventricle, as in some patients with myocardial infarction, quinidine or pronestyl may terminate the paroxysm with satisfactory restoration of a normal rhythm. If complete heart block is present, however, abolition of the ventricular tachycardia may leave the heart without a pacemaker; the result, cardiac standstill. It is better to treat ventricular tachycardia in such a patient by other measures.

DR. READER: Such as what?

DR. LUCKEY: Digitalis appears to be helpful in some of these. It may be by increasing the coronary flow.

DR. GOLD: I would like to suggest an alternate solution to this problem. As the majority of cases of ventricular tachycardia present themselves, we have no means of knowing whether complete heart block co-exists or not. In a few cases I have pursued a plan which I now believe is the method of choice for all cases of ventricular tachycardia. The dosage of quinidine is so arranged as to produce progressive slowing of the idioventricular rhythm without aiming at direct

abolition of the abnormal rhythm. As one follows the condition closely, the ventricular rate may slow from 180 to 140, then down to 110, then to 90, and so on. If these changes are followed by means of the electrocardiogram, one will often observe that at the lower rates normal rhythm has already been established. Frequently, however, there is still an idioventricular rhythm even at the very low rates of 60 or 70 a minute, signifying that no active pacemaker other than the focus for the ventricular tachycardia is at the time available in the heart. It also happens that if the rate is maintained at the lower levels of 90 or 100 for a day or two, normal beats of sinus rhythm will begin to appear in the electrocardiogram. This plan of treatment avoids the risk of leaving the heart without a pacemaker upon abrupt cessation of an ectopic pacemaker. There are some physiologic experiments which show that a very rapid ectopic rhythm tends to suppress pacemaking in the rest of the heart for a considerable period and that dormant pacemakers become active if the ectopic rhythm is maintained for some time at a slow rate.

SUMMARY

DR. GOLD: The various aspects of quinidine therapy were explored in this conference: types of patients in which it is useful, types of clinical problems to which attention is directed, plans of dosage, toxic effects, sources of danger, methods for reducing the risks and such other matters relating to the subject as emerge from extensive experience. Quinidine therapy is directed against only one aspect of heart disease, namely, disorders of rhythm, and with varying degrees of efficiency it is useful in all the auricular and ventricular ectopic rhythms. It was pointed out that the treatment of a paroxysm is a somewhat different problem from that of prevention of recurrences. The details for each were discussed. The nature of the untoward events during a course of quinidine therapy, the case of chronic auricular fibrillation and of ventricular tachycardia received special attention. A thorough familiarity with the problems elaborated in this conference should add materially to the efficacy and safety of treatment with quinidine.

Clinico-pathologic Conference

Hyperthyroidism, Possible Malignancy, Liver Disease and Therapeutic Myxedema

STENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. B. (No. 221942) an unemployed Negress, thirty-seven years of age, was admitted to the Barnes Hospital for the first time on April 21, 1953, with a chief complaint of swelling of the legs and abdomen for four months. She had previously been well except for recurrent bouts of sore throat which were moderately severe and tended to recur two or three times a year; they were associated with tender, enlarged cervical lymph nodes. At no time were the episodes followed by sore joints or urinary symptoms. For one year before admission the patient had noted mild dyspnea on exertion, but otherwise had felt well. She denied orthopnea or nocturnal dyspnea. About four months before admission both knees became tender, painful and swollen. The swollen joints subsided rapidly, but shortly thereafter the patient noted gradually increasing edema of the ankles which progressed to involve the legs and then the abdomen. About one week prior to entry she found that she needed two pillows in order to sleep comfortably, and often awakened at night because of dyspnea, wheezing and cough which occasionally were productive of small amounts of blood-flecked sputum. The patient was seen by a private physician who gave her tablets and capsules which she took until admission. She had had some night sweats during the present illness, but although she had not taken her temperature, she did not think that she had fever and she had not had chills.

Past history revealed that three years ago the patient had an episode of burning on urination and back pain; she was told that she had pus in her urine, and responded to symptomatic treatment. Two years before admission she had a cough productive of white sticky sputum for three months. However, a chest x-ray taken then and another a year before admission were said to have been negative. She had no persistent cough or weight loss. A year before admission the patient received twenty injections, ten of them intravenously and ten intramuscularly, because she had a positive serologic test for syphilis. The personal and social history were non-contributory.

Physical examination revealed a temperature of 37.6°C., pulse 55 to 95, respirations 25 and blood pressure 125/70. The patient was a well developed, well nourished woman who was able to breathe comfortably only when sitting erect. Her skin was clear. The pupils were equal in size and reacted normally to light and accommodation, and the eye grounds showed no abnormalities. Examination of the upper respiratory tract was negative. The neck veins were engorged. The thyroid gland was not palpated, but the trachea seemed deviated to the right. There was no lymph node enlargement. Signs of fluid in both pleural cavities were elicited, greater on the left, and the mediastinum was shifted slightly to the right. No rales were heard. The heart was enlarged and the apical impulse diffuse. The rhythm was "irregular" and not otherwise characterized. A grade II to III blowing systolic murmur was heard at the apex; no diastolic murmurs were heard. The abdomen was bulging and tense, and signs of free fluid were present. The liver was not felt, but one observer thought he could percuss an enlarged spleen. The abdominal wall was edematous and there was marked edema of the lower extremities extending above the iliac crests. Pelvic and rectal examinations were not remarkable. Neurologic examination was within normal limits except for absence of abdominal reflexes.

The laboratory data were as follows: red blood cells, 4,900,000; hemoglobin, 13.5 gm. per cent; white blood cells, 7,300; differential: segmented neutrophils 67 per cent, lymphocytes 28 per cent, eosinophils 2 per cent, monocytes 2 per cent. Urinalysis: specific gravity, 1.030; pH, 6; albumin, negative; sugar, negative; centrifuged sediment, negative. Stool: guaiac negative. Cardiolipin test: negative. Blood chemistry: non-protein nitrogen, 18 mg. per cent; fasting blood sugar, 78 mg. per cent; sodium, 129.4 mEq./L; chloride, 104 mEq./L.; total protein, 7.3 gm. per cent; albumin, 3.3 gm. per cent; globulin, 4.0 gm. per cent; thymol turbidity, 5.8 units; cephalin-cholesterol flocculation, 3+; alkaline phosphatase, 18.4 Bodansky units; prothrombin time, 48 per cent of normal; total bilirubin, 5.72 mg. per cent, with the one minute reading 1.8 mg. per cent; amylase, 114 Somogyi units. Venous pressure, 305 mm. of saline; circulation time (decholin®): 26 seconds. Sedimentation rate: 38 mm. per hour. Roentgenogram of the chest: pleural effusion on the left and questionably on the right, markedly enlarged globular cardiac silhouette thought to represent pericardial effusion. Intravenous pyelogram showed evidence of ascites. There was prompt appearance of dye and moderate concentration at five minutes. Incomplete filling of the renal collecting systems on both sides was noted with a suggestion of some clubbing of the calyces in the lower pole of the left kidney. Gastrointestinal series: evidence of ascites, depressed left kidney; enlarged retroperitoneal lymph nodes were suggested. The barium enema was negative. Electrocardiogram: auricular fibrillation, low voltage, digitalis effect, indeterminate heart position. PPD test: negative first and second strength. Histoplasmin skin test: negative.

During the early weeks of hospitalization considerable effort was made to characterize the serous effusions. These data are summarized in Table 1. In addition, routine cultures of the fluids were sterile, and two cultures of the pleural fluid and one of pericardial fluid were negative for tubercle bacilli. The left pleural fluid was variously described as bloody, serosanguineous and chylosanguineous. The cholesterol content of pleural fluid on May 1, 1953, was 29 mg. per cent. Early in May a small firm nodule was described in the left lobe of the thyroid and confirmed by several observers. It was noted that the distended veins over the face and the retinal veins were pulsating. Despite the anasarca the patient was no longer orthopneic. One observer described a low-pitched rumbling diastolic murmur at the apex and suggested mitral stenosis. Another observer considered this to be a "sound" and not a murmur. On May 20th pericardiocentesis was done and yellow-brown fluid obtained. Lymph nodes in the left axilla were excised and reported as showing "hyperplasia." The basal metabolic rate was +42 and +39 per cent. With a venous pressure of 270 mm. of saline, the circulation time was now 8 seconds. Radioactive iodine uptake was done. Eighty-five per cent of the I-131 was retained by the patient; urinary excretion was 9.5 per cent. The left chest and precordium were scanned with a Geiger counter, which demonstrated increased radioactivity over both sites. Protein-bound iodine was 14.8 gamma per cent, blood cholesterol 112 mg. per cent. The patient was

TABLE 1
CHARACTERISTICS OF SEROUS FLUIDS

Date	Source	Amount (ml.)	Specific Gravity	Protein (gm. %)	White Blood Cells (per cu. mm.)	Red Blood Cells (per cu. mm.)	Cytology	Cell Block
4/21	Left pleural	1,000	<1.025	3.7	"o"	8,360	.....	.....
4/23	Left pleural	1,000	1.017	3.2	6,950	36,400	Negative	Atypical cells
4/24	Left pleural	1,000	1.011	...	6,800	.....	"Suspicious"	Atypical cells
4/28	Left pleural	1,160	1.017	2.3	110	16,350	"Positive"	Atypical cells
5/1	Left pleural	1,400	.....	...	.....	.....	"Positive"	Suspicious
5/20	Pericardial	350	1.015	2.3	190	.....	.....	Suspicious cells
5/28	Left pleural	860	1.008	1.8	2,504	80,050	.....	Atypical cells
6/29	Peritoneal	600	1.015	3.5	3,350	19,300	.....	Suspicious cells
7/5	Peritoneal	1,700	1.011	3.4	2,700	10,500	.....	"Carcinoma"

given 10 mc. of radioactive iodine as a therapeutic dose. She was again scanned and there was increased activity over the left chest as well as over the left axilla where the surgical biopsy had been taken. A second dose of 20 mc. of radioactive iodine was given two weeks after the first. A basal metabolism rate taken two days later was +29 per cent.

Conversation with the patient's private physician revealed that she had been digitalized and was receiving 0.2 mg of digitoxin daily. She had also taken a mercurial diuretic orally. Because of the slow auricular fibrillation and signs of digitalis effect on the electrocardiogram, digitalis was initially withheld. Repeat electrocardiograms were unchanged, as were roentgenograms of the chest. On the thirty-ninth hospital day the patient was redigitalized but, in spite of this, pleural and ascitic fluid slowly reaccumulated. Her course in the hospital was febrile, temperature elevations ranging between 38 and 39°c. daily. White blood counts were all within normal limits and one blood culture was negative. She was discharged on July 6, 1953, the fifty-seventh hospital day, with fluid still present in the left pleural and peritoneal cavities. Histologic examination of sediment and cell blocks from ascitic fluid obtained shortly before discharge was interpreted as compatible with carcinoma. Additional laboratory studies at this time were as follows: venous pressure, 195 mm. of saline; circulation time (decholin), 32 seconds; cephalin-cholesterol flocculation, 3+; thymol turbidity, 6.4 units; alkaline phosphatase, 7.8 Bodansky units; total protein, 6.9 gm. per cent; albumin, 3.1 gm. per cent; globulin, 3.8 gm. per cent; bromsulfalein retention, 33 per cent at forty-five minutes. The patient was discharged on a maintenance dose of digitalis and a low-salt diet and was followed in the outpatient clinic. She initially gained weight, and edema and ascites became more pronounced. Dosage of digitalis and mercurial diuretics was increased. Subsequently, the patient exhibited marked improvement, and one month after discharge a repeat chest x-ray showed complete resorption of the bilateral pleural effusions. An electrocardiogram taken at that time revealed sinus rhythm, abnormal form of ventricular complex and digitalis effect. Clinic notes through August 18th mention decreasing jaundice and thereafter fail to mention its presence at all. On September 30, 1953, liver function tests were reported as follows: bromsulfalein retention, 40 per cent at forty-five minutes; cephalin-cholesterol flocculation, 3+; thymol turbidity, 9.7 units; albumin, 3.4 gm. per cent; globulin, 4.6 gm. per cent; alkaline phosphatase, 15.5 Bodansky units. In September the patient was given 10 mc. of I-131. On October 28th the protein-bound iodine was reported as 14.8 gamma per cent, but on November 24, 1953, the basal metabolic rate was +2 per cent and the protein-bound iodine had fallen to 2.9 gamma per cent. Digitalis was discontinued; although cardiac enlargement persisted, the rhythm remained regular. Neither ascites nor ankle edema was present. At about that time the patient began to complain of nervousness. She also noted puffiness of the face and said that she felt sluggish and tired. Her appetite became poor.

Three weeks before admission she was markedly anoretic and vomited several times. She complained of weakness and nervousness. Three days prior to entry she became increasingly lethargic and her family noted that she was confused. Chest x-ray taken five days before admission was negative; the heart size was normal. For about four days she had eaten almost nothing, and she was readmitted to the hospital on January 17, 1954, for re-evaluation. At that time her temperature was 37°c., pulse 56, respirations 12, and blood pressure 116/80. She was very lethargic, lay flat in bed and was not oriented as to place or time. "Fetor hepaticus" was described by one observer. The skin was dry with poor turgor. There was a questionably icteric tint to the sclerae and mucous membranes. The fundi were normal. The neck was supple and the thyroid not palpable. There was no venous engorgement. The lungs, except for a few wheezes at both bases, were clear. The heart was enlarged, the left border of cardiac dullness extending 13 cm. to the left of the mid-sternal line. There was questionable mediastinal widening. A soft blowing systolic murmur was heard at the base. The liver was palpable about 1 cm. below the costal margin. The spleen was not felt. There was no evidence of ascites. Rectal and pelvic examinations were within normal limits. There was a trace of pretibial edema bilaterally. There was a coarse, flapping tremor of the outstretched hands. Coordination was poor. Sensory examination was incomplete because the patient was so obtunded. Tendon reflexes were hyperactive.

The laboratory data were as follows: red blood count, 4,860,000; hemoglobin, 15 gm. per cent; white blood cells, 5,900; differential: segmented neutrophils 53 per cent, eosinophils 2 per cent, basophils 1 per cent, non-segmented neutrophils 5 per cent, lymphocytes 36 per cent, monocytes 3 per cent. Urinalysis: specific gravity, 1.019; pH, 5.5; albumin, trace; sugar, trace; centrifuged sediment: two to three white cells and an occasional red blood cell per high-power field. Cardiolipin test: negative. Blood chemistry: non-protein nitrogen, 18 mg. per cent; sodium, 136.7 mEq./L.; potassium, 2.4 mEq./L.; chloride, 88 mEq./L.; carbon dioxide combining power, 35.3 mEq./L.; cholesterol, 390 mg. per cent; total bilirubin, 2.56 mg. per cent, with the one minute fraction 0.74 mg. per cent; total protein, 7.5 gm. per cent; albumin, 3.6 gm. per cent; globulin, 3.9 gm. per cent; cephalin-cholesterol flocculation, 3+; thymol turbidity, 8.5 units; alkaline phosphatase, 14.5 Bodansky units; prothrombin time, 52 per cent; protein-bound iodine, 1.2 gamma per cent; bromsulfalein, 55 per cent retention at forty-five minutes. Electrocardiogram: sinus rhythm, abnormal form of ventricular complex, low voltage compatible with pericarditis, prolonged auriculoventricular conduction (0.19–0.24 seconds). Fractional bromsulfalein clearance: 51 per cent retention at thirty minutes, with slow excretion interpreted as compatible with infiltration of the liver by tumor. Cerebrospinal fluid: initial pressure, 430 mm. of saline; final pressure 180 mm. after removal of 5 mm. of fluid; cells: one lymphocyte; protein, 65 mg. per cent.

The patient was given glucose intravenously as well as sodium monoglutamate, without change in her status. The day after admission she began to complain of severe bilateral frontal headache. Shortly thereafter she was noted to have irregular respirations, associated with periods of stupor. Periods of apnea became noticeable and more marked. An endotracheal tube was inserted and an Emerson respirator was used to maintain ventilation. Blood began oozing from a lumbar puncture and venipuncture sites. The patient was seen by a neurosurgical consultant, who thought that evidence of increased intracranial pressure was not convincing. No surgical intervention was thought advisable because of the poor status of the patient. In spite of supportive therapy, the patient rapidly became completely comatose. The blood pressure fell and, though maintained by nor-epinephrine for a short time, became unobtainable, and the patient expired on January 19, 1954, the third hospital day.

CLINICAL DISCUSSION

Dr. Virgil Scott: In the discussion of this case I shall not take the time which would be needed to review the welter of information both clinical and laboratory included in the protocol. Suffice it to say for summary purposes, the patient was a thirty-seven year old woman who apparently had a rare type of cancer, carcinoma of the thyroid, with functioning metastases in various sites. The present illness was of brief duration. She was apparently well until four months before her first admission when, after a bout of pain in the knees, edema developed which became progressively more severe. She also noted dyspnea and orthopnea, and in this state was admitted to the hospital.

Physical examination showed anasarca, with massive pitting edema to the level of the breasts. There was clinical evidence of fluid in both pleural cavities, most of it on the left, and ascites. In all likelihood fluid was probably also present in the pericardial sac, although its presence was not suspected until later. The heart was described as enlarged, with a grade II to III systolic apical murmur and auricular fibrillation. Except for the ascites the abdominal examination was unrevealing. One observer thought that he could percuss an enlarged spleen.

The admission laboratory data showed evidence of liver dysfunction, a high venous pressure, a prolonged circulation time and an elevated sedimentation rate. The protocol indicates that a great deal of effort was expended in trying to determine the nature of these serous effusions, and I think members of the house staff deserve a great deal of credit for the persistence with which they approached this problem. They were able to confirm the fact that there were cancer cells in the left pleural fluid and finally in the ascitic fluid. The presence of metastatic cancer was also confirmed by the use of the Geiger counter, which, after the administration of radioactive iodine, demonstrated radioactivity to be present in increased amounts over the left chest and over the precordium.

The patient was treated with radioactive iodine, but at the time of discharge her condi-

tion was essentially as it had been at the time of admission except that she was less edematous.

She was followed in the Outpatient Department, and after a few weeks began to do very well. She became free of edema and of the fluid in the serous cavities. Her cardiac rhythm reverted to normal and she began to gain weight which was solid flesh. Then, about one month before her second admission, she again developed clinical evidence suggestive of cancer, and her condition deteriorated rapidly.

At the time of the second and last admission on January 17, 1954, there were neurologic manifestations suggestive of increased intracranial pressure, and a roentgenogram of the chest demonstrated the presence of radiolucent lesions in several ribs. Fractional bromsulfalein clearance was compatible with metastatic tumor in the liver. She failed rapidly and expired on January 19, 1954. I have worded this summary as I have deliberately, because if one reads the protocol and accepts the opinion of the majority of the patient's physicians, he must conclude that it presents the course of events as they occurred. There is, however, reason to be suspicious of the diagnosis which was made, and in our discussion the evidence bearing on the question of whether the patient had cancer of any organ at any time should be examined critically. Dr. Elliott, will you begin by demonstrating the x-rays?

Dr. Gladden V. Elliott: I am glad Dr. Scott qualified his summary as he did because I would like to modify some of the radiologic interpretations. First, it will be well to review a selected series of examinations of the chest merely to demonstrate the rather dramatic change in the radiographic findings which took place from the time the patient was first seen in April, 1953. At that time there was a massive pleural effusion on the left, and a cardiac silhouette which was tremendously enlarged; the left border could not be seen, and the right border extended well into the right lung field. The possibility of a pericardial effusion was suggested. Two days later, after two thoracenteses, the left pleural effusion was decreased, and consequently it was easier to appreciate the size of the cardiac silhouette, which was extremely large, globular in shape and compatible with pericardial effusion. The presence of pericardial fluid was confirmed a few days later, and following a pericardial paracentesis a film showed air in the pericardium sac and further reduction in the pleural effusion and in the size of the heart.

Approximately four months after the initial examination there was little or no evidence of remaining pericardial fluid; some mild vascular congestion persisted and the heart had further decreased in size. Prior to the patient's last admission in January, 1954, she had completely resorbed all of the pleural fluid, and the cardiac silhouette had been reduced to reasonably normal size; pulmonary congestion had disappeared and the lung fields were clear. The lateral view at that time did indicate some posterior displacement by what appeared to be an enlarged left ventricle, but the change in findings toward the normal was dramatic indeed.

The radiologic findings pertaining to the abdomen were also of interest. On the pyelograms, the kidneys were poorly visualized and the left was lower than the right, a finding opposite to that seen normally. Evidence of ascites was also noted. A gastrointestinal series suggested that the fundus of the stomach was depressed below the level of the diaphragm; again, floating intestinal loops congregated in the central abdomen were indicative of ascites. Displacement of the splenic flexure inferiorly was demonstrated by the barium enema; this finding, taken with the low left kidney, was compatible with a left upper quadrant mass. Finally, a word in regard to the report of radiolucent areas in the fourth, fifth and sixth ribs on the right. I have carefully reviewed the particular film on which the report was based with the initial previewer; both of us now agree that there is no convincing evidence of metastatic lesions. Many other attempts were made to demonstrate bony destruction or other evidence of metastatic tumor and none was successful.

Dr. Scott: Dr. Ackerman has kindly consented to enter into the discussion and will review some of the experience in the Surgical Pathology Laboratories with exfoliative cytology and cell block sections.

Dr. Lauren V. Ackerman: As we have emphasized previously, the problem of interpreting the nature of exfoliated cells or cells in fluid from body cavities is a most difficult one, and in our laboratory, we believe definite significance attaches chiefly to a positive diagnosis. Over a period of two years, Dr. Takagi reviewed all the fluids from 136 patients for whom we had some form of pathologic confirmation, i.e., by biopsy, exploration or autopsy. Fifty proved not to have

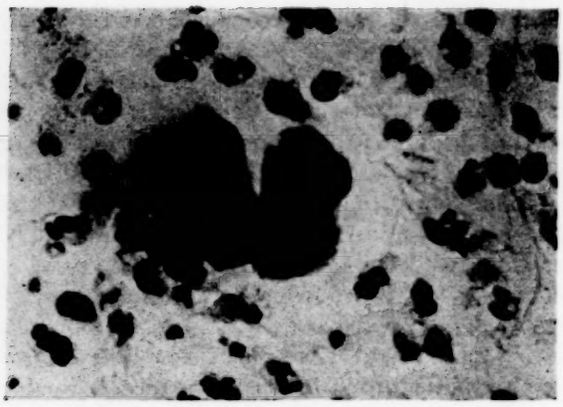

FIG 1. A collection of large cells with dark and irregular nuclei from the sediment of the ascitic fluid examined after paracentesis. These cells and their configuration are indistinguishable from carcinoma.

neoplasms, while eighty-six did have malignant disease. In the latter group, specimens were called positive in 45 per cent, suspicious in 10 per cent and negative in 45 per cent. The designation "suspicious" is obviously not helpful to the clinician. There was one false positive in the series in a patient with liver cirrhosis, and since 1948 to the present time we are aware of three additional errors; of these, one patient had a mesothelioma, whereas our diagnosis was mesothelial proliferation. The other two patients had cirrhosis of the liver. It is worth pointing out in this regard that marked proliferation of the mesothelium is common in patients with long-standing ascites, and the cells which result often resemble carcinoma cells closely. In our whole series, we made an erroneous diagnosis of cancer in 0.7 per cent.

The case under discussion here was an extremely interesting one. Figure 1 is from the cell block of ascitic fluid on which we made a diagnosis of cancer. The nuclei are multi-shaped and deep staining, and I would in retrospect hold the same opinion as I did originally, namely, that the cells are malignant.

DR. SCOTT: Let us now turn to consideration of the status of the patient's thyroid gland, after which we can return to the possibility of its having been the site of malignancy. At the outset it should be mentioned that on April 24th the patient had an intravenous pyelogram which may or may not be of significance in respect to the I-131 studies. On May 28th 100 mc. of radioactive iodine were given, the uptake was 85 per cent, the excretion 9.5 per cent. Three days later, on June 1st, the protein-bound iodine was 14.8 gamma per cent. Dr. Eisenstein, I hope that you will comment on the effect of the iodine-containing dyes used in intravenous pyelography and cholecystography on protein-bound iodine levels. Also on June 1st the basal metabolic rate was +42 per cent and +39 per cent. Unfortunately the patient's temperature was not recorded but judging from the temperature record in her chart, one can presume it was not significantly elevated. You will recall, however, that she was suffering from severe congestive failure, which may well have influenced the basal metabolic rate. Three days later, on June 4th, she received double the initial tracer dose of radioactive iodine and the uptake was approximately 100 per cent. She was then given therapeutic doses totalling 98 mc. over a period of two months. The basal metabolic rate gradually fell. Radioactive iodine studies were repeated twice subsequently and increasing excretion of isotope was demonstrated, 66.5 per cent on August 8th and 72 per cent on September 6th. On October 28th the protein-bound iodine was still at the same level, 14.8 gamma per cent, but then fell precipitously to 2.9 gamma per cent, and finally, just before the patient's death, to 1.2 gamma per cent. Dr. Eisenstein, will you discuss these findings?

DR. ALBERT B. EISENSTEIN: There is ample evidence from the laboratory data you have reviewed to indicate that the patient was hyperthyroid early in her course. The protein-bound iodine remained elevated until late in October, although she received therapeutic doses of radioactive iodine totalling 98 mc. in the previous several months. When was the last dose given?

DR. SCOTT: On August 12th at which time she received 50 mc.

DR. EISENSTEIN: Despite the fact that the protein-bound iodine remained elevated until late October, there was a progressive increase in the amount of the tracer dose excreted in the urine, which indicates to me that during this interval there was some decrease in production of thyroid hormone. Then, very late in the course, the protein-bound iodine fell sharply to a very low value and I would conclude that the treatment ultimately led to hypothyroidism. The basal metabolic rate returned to within a normal range. With regard to the effect on I-131 uptake of dyes used for pyelography and cholecystography, it has been noted that these substances, which contain organic iodides, may interfere markedly with the uptake of I-131 by the thyroid gland, more so in patients who are euthyroid than in those with hyperthyroidism. Thus in this case the value of 14.8 for the initial

protein-bound iodine determination may have been due in part to the fact that the patient received urokon® on April 24th. However, the tracer studies indicating an uptake of 85 per cent substantiate increased production of thyroid hormone.

DR. SCOTT: Is there any further discussion with reference to the presence of hyperthyroidism?

DR. WILLIAM H. DAUGHADAY: The clinical picture in this woman did not actually support the diagnosis of hyperthyroidism as well as did the laboratory findings. Her skin was relatively cool and her pulse, although irregular, was quite slow.

DR. VIRGIL LOEB, JR.: Do mercurial diuretics affect the protein-bound iodine?

DR. DAUGHADAY: The protein-bound iodine is lowered abruptly by administration of mercurial diuretics, so caution is necessary in evaluation of this test of cardiac patients. One ought to allow at least three days for the mercury to be excreted before one measures the protein-bound iodine. The explanation for the interference is that mercury inhibits the reduction of ceric sulfates and thus alters the color reaction used to determine protein-bound iodine.

DR. SCOTT: It seems clearly established at least from the laboratory data that this patient had hyperthyroidism. One of the other confusing questions concerned her cardiac status. It was thought on some occasions, because of the presence of certain murmurs, that she had rheumatic heart disease. The heart was very large, with a grossly irregular rhythm identified as auricular fibrillation. Dr. Bercu, do you think the patient's heart disease was secondary to hyperthyroidism or due to some other etiology?

DR. BERNARD BERCU: It would be difficult to answer your question unequivocally. Since there was disagreement as to the murmurs present, and in view of the over-all picture and of the fact that peculiar diastolic sounds have been frequently described in the presence of pericardial effusions, I would conclude that the patient probably had a pericardial effusion without significant valvular disease. This conclusion is supported by the absence of murmurs after cardiac function improved. Pericardial effusions are seen in uremia, myocardial infarction, either tuberculous or other bacterial infections, and rheumatic fever, but none of these seems likely in this case. The benign idiopathic form of pericarditis is also most improbable, and by exclusion infiltration of the pericardium by malignancy suggests itself as most compatible with the clinical picture as a whole.

DR. SCOTT: Dr. Daughaday saw this patient and was one of the first to suggest the diagnosis of thyroid carcinoma. I would like him to outline for us the factors which led him to propose that explanation.

DR. DAUGHADAY: One of the most convincing findings in favor of the diagnosis of cancer was the presence of cells in the pleural and ascitic fluids that were variably interpreted as "atypical" to "malignant." The disparity between the clinical and laboratory findings regarding hyperthyroidism, and the readily palpable nodule in the thyroid gland, made the diagnosis of thyroid malignancy more likely.

DR. SCOTT: Dr. Elliott, would you comment on the use of the Geiger counter exploration in a case such as this one?

DR. ELLIOTT: We made three attempts to demonstrate functioning thyroid metastases by Geiger counter scanning. It should be pointed out that none of our detectors is sufficiently columnated to afford accurate appraisal of the uptake or lack of uptake of I-131 by lesions very close to the thyroid gland itself. In this instance on June 1, 1953, detectable radioactivity in the left chest was somewhat greater than that in the right. In addition, the uptake was higher in the midline than it was on the right. This observation could be explained by the presence of functioning metastatic tumor in the left pleura. On the other hand, this patient did have a nodule in the left lobe of the thyroid and that nodule, if it had been functioning alone, could explain the disparity in radioactivity over the two sides of the chest. At a subsequent examination in September there was a uniform activity over the entire body, all at a low level, and the uptake over the thyroid itself was markedly decreased. Prior to the latter study, she already had had 98 mc. of radio-iodine. We thus failed to obtain evidence of functioning metastases, and I doubt that the evidence at hand can be considered a reliable indication that there was such a metastasis in the left pleural space.

DR. SCOTT: One of the other findings favoring the diagnosis of cancer was fractional bromsulfalein clearance terminally. Dr. Mendeloff, would you comment on this test?[1]

[1] INGELFINGER, F. J., BRADLEY, S. E., MENDELOFF, A. I. and KRAMER, P. Studies with bromsulfalein. I. Its disappearance from the blood after a single intravenous injection. *Gastroenterology*, 11: 646, 1948.

DR. ALBERT I. MENDELOFF: I did not see this patient; but when I was asked whether her fractional bromsulfalein clearance was compatible with metastatic carcinoma of the liver, my answer was yes. The curve representing the rate of clearance was not given by a straight line; rather it deviated in the manner which is associated, in non-jaundiced patients, with infiltration of the liver by fat or especially by tumor. The total bilirubin was 2.5 mg. per cent at the time; and although the other laboratory findings were compatible with cirrhosis, cirrhotic patients whose bromsulfalein retention is of the order noted here—55 per cent—are usually more deeply jaundiced. I need not emphasize that the diagnosis of cancer of the liver cannot be made on bromsulfalein clearance *per se*, but nevertheless curves of the type seen in this case are encountered in 90 per cent of patients who have infiltration of the liver.

DR. SCOTT: The liver function studies were of interest in their uniformity over the period in which the patient was followed. Despite the fact that the bromsulfalein clearance was typical of that seen when the liver is the site of infiltration by tumor, I find it hard to believe that the other tests of liver function would not have shown a more changing pattern had the patient had tumor. We have agreed that she had hyperthyroidism and congestive heart failure, but control of these failed to alter the pattern of the liver function studies. Dr. Shank, will you give us your views on this apparent paradox.

DR. ROBERT E. SHANK: The evidence of hepatic damage is clear-cut, and it must be presumed, therefore, that the liver was abnormal, even though it was palpated on only one occasion.

DR. SCOTT: It was not felt, Dr. Shank, at the time of admission, but later, during the patient's first hospital stay, it was palpable 2 cm. below the costal margin and remained at that level thereafter.

DR. SHANK: Ordinarily with metastatic liver disease there is greater enlargement of the liver than was apparent in this case. On that basis, it is reasonable to suggest that some other form of liver disease should be considered. Since this patient was hyperthyroid, it is pertinent that cirrhosis may be associated with thyrotoxicosis; it has been extensively studied by Moschcowitz.[2]

[2] MOSCHCOWITZ, E. Pathogenesis of cirrhosis of the liver occurring in patients with diffuse toxic goiter. *Arch. Int. Med.*, 78: 497, 1946.

In this form of cirrhosis the liver is ordinarily not greatly enlarged. As I recall, in Moschcowitz's series, the liver weights varied from about 800 to 1,200 gm., less than one would have anticipated from the weights of the given patients. According to Moschcowitz, cirrhosis in thyrotoxicosis is characterized primarily by vascular changes and fibrosis in the subcapsular regions of the liver. Later there is progressive fibrosis, not wholly analogous to the fibrosis associated with portal cirrhosis, for in portal cirrhosis lobules of the liver may be entirely encircled by the increased fibrous tissue, whereas in thyrotoxic cirrhosis there are simply stellate formations of fibrosis. Moschcowitz postulates that the latter change is due to increased velocity of blood coursing through the hepatic artery, and to the opening of anastomotic channels which are known to exist between the portal vein and hepatic artery. Ultimately, thickening of the vessels and fibrosis about them is induced. To date experimental evidence to substantiate Moschcowitz's hypothesis is lacking. Many attempts have been made to induce hepatic damage or cirrhosis by thyroid feeding; but although necrosis in the liver has been described in animals so treated, it has not been of uniform type and cirrhosis has not developed. This patient could have had cirrhosis of the type associated with thyrotoxicosis; and since she also had congestive heart failure, some element of cardiac cirrhosis may be found. On the other hand, one would have anticipated that the liver at one stage or another would have been greatly enlarged.

DR. SCOTT: One final question, Dr. Shank; did the patient die in hepatic coma?

DR. SHANK: I don't know. She is described as having exhibited a flapping tremor which can be associated with pre-coma in patients suffering from hepatic necrosis. Furthermore, a bleeding tendency developed terminally which is frequent in hepatic coma. On the other hand, although the cerebrospinal fluid pressure may be slightly increased in hepatic coma, the very high pressure seen here was far higher than what one would have expected, and should lead us to consider a lesion within the central nervous system.

DR. SCOTT: There are three possibilities, it seems to me, in respect to the cause of death. One, hepatic coma, has been dealt with by Dr. Shank; another, about which there is little to say, is a metastatic intracerebral lesion; the third is that the terminal episode represented "gallop-

ing myxedema," with coma on that basis. Dr. Recant, what about the latter explanation?

DR. LILLIAN RECANT: When we saw this patient during the last admission, we were very impressed by the clinical features which she presented. There was marked puffiness around the eyes, the skin was very dry and her demeanor was sluggish. From the history it seemed that lassitude had been present for a month. Knowing also that the patient had received large doses of radio-iodine and that the protein-bound iodine had fallen to 1.2 gamma per cent, we were convinced that thyroid function was at myxedematous levels. As you have indicated, Dr. Scott, in cases of "galloping myxedema" the cerebrospinal fluid pressure may be greatly increased, so that this explanation of the terminal event is a reasonable one. We saw a similar case not long ago in which no other cause of distinctly increased intracranial pressure could be found at autopsy.

DR. SCOTT: It is the consensus, I believe, that the patient did have hyperthyroidism, and that much of her clinical course can be explained on that basis. She was treated with radioactive iodine with recovery, but unfortunately severe myxedema developed terminally. Most of those who saw her also believed she had cancer of the thyroid, although our discussion today does not firmly support this view.

Clinical Diagnoses: Thyrotoxicosis, treated with I-131; myxedema due to I-131 treatment of hyperthyroidism; carcinoma of the thyroid with metastases to liver, brain, pericardium, pleura and peritoneum.

PATHOLOGIC DISCUSSION

DR. JOHN M. KISSANE: The peritoneal and pericardial cavities at autopsy contained 30 ml. of clear yellow fluid. Except for focal fibrous adhesions between the liver and diaphragm, the serosal surfaces were smooth and glistening. No neoplasms were seen. The thyroid was greatly reduced in size and weighed only 10.5 gm. It was composed of tough, gray, fibrous tissue with a coarse and indistinct lobular pattern in which there was very little of the normal mahogany thyroid parenchyma recognizable. Above the left lobe there was an isolated nodule of more normal-appearing thyroid tissue which apparently had been isolated by the process of fibrosis. The heart weighed 325 gm. and except for this minimal enlargement showed no significant abnormalities. The spleen was slightly enlarged and congested. The liver, as shown in Figure 2, was enlarged to a weight of 1,450 gm. The capsular surface was finely granular. The cut surface displayed a rather uniform fine nodularity and the consistency of the organ was increased. The brain was of normal configuration. The convolutions were slightly flattened and the tissue seemed to be softer than usual throughout.

FIG. 2. The liver showing the diffuse nodularity of the cut surface indicating a cirrhosis of the diffuse nodular type.

DR. DAVID E. SMITH: The only essential gross findings were an atrophic and fibrotic thyroid and cirrhosis of the liver. Search for the tumor that was suspected clinically was unsuccessful. The only possible site of tumor seemed to be in the atrophic thyroid where a tumor might have been largely destroyed by the therapy with radioactive iodine. Figure 3 is a section of the thyroid and shows that the epithelial elements have been reduced to small groups that form indistinct acini embedded in a large amount of fibrous tissue. This section was from the center of the gland and should have shown the normal architecture of the thyroid had such been present. Many of the cells show the very large and irregular nuclei which are typically found in thyroids that have been treated with radioactive iodine. There is no clear evidence that there ever was a carcinoma within this gland. The histologic picture that is present could have represented the effect of a large dose of radioactive iodine on a hyperplastic or normal thyroid, although the latter is considerably less likely, since extensive fibrosis is difficult to induce in the normal gland by such means. Figure 4 is from the nodule which was above the left lobe of the thyroid. It has the appearance of a degenerated nodule in a nodular goiter. The enlarged acini are preserved and there are foci of calcification. The persistence of the normal histologic appearance of this nodule is probably related to the fact

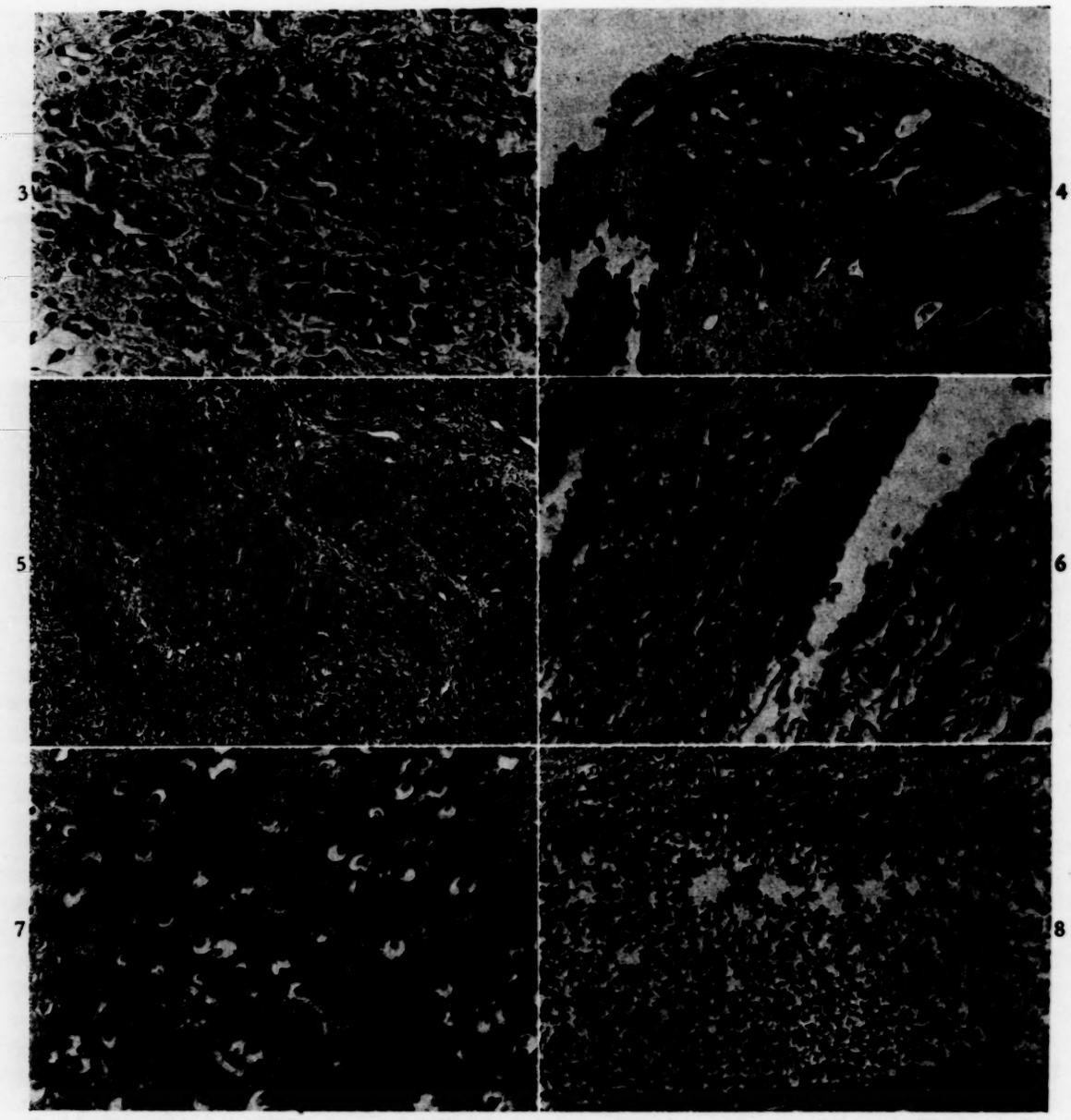

FIG. 3. Thyroid showing diffuse interstitial fibrosis and disruption of the acinous architecture. The epithelial cells show large, irregular and dark nuclei typical of the status following radioactive iodine therapy.

FIG. 4. The nodule from the left superior portion of the thyroid which is a relatively unaffected nodule of a nodular goiter and shows various degenerative reactions.

FIG. 5. Cirrhosis of the liver with diffuse confluence of portal spaces and hyperplastic regenerated lobules.

FIG. 6. A diverticulum of the peritoneum in the capsule of the liver showing hyperplastic mesothelial cells which are the source of the desquamated cells that can be confused with carcinoma in ascitic fluid.

FIG. 7. The cerebral cortex showing widened pericellular and paravascular spaces suggestive of edema and the disappearance or poor-staining of neurons with satellitosis and gliosis suggestive of the diffuse destruction of nerve cells.

FIG. 8. The granular layer of the cerebellum showing almost complete dissolution of the granule cells. This change is possibly at least in part an artefact, but the good preservation of Purkinji cells and glial cells on each side of the granular layer suggests an antemortem preparation for rapid autolysis if not actually intravitam destruction of neurons.

that such nodules often do not absorb the radioactive iodine and therefore are not rendered atrophic or fibrotic by the treatment. This nodule, therefore, was presumably not functional, but it was quite obviously the one that was palpated in the neck of the patient.

Figure 5 is an illustration of a section of the liver and shows fairly typical diffuse nodular cirrhosis. There are large bands of fibrous tissue that run between the portal spaces and isolate lobules, many of which are frankly hyperplastic. These alterations cannot be considered as being different from the usual types of diffuse nodular cirrhosis. More particularly, they do not seem to be the type of alteration described as thyrotoxic cirrhosis. Figure 6 is from the capsule of the liver and shows a small diverticulum of the peritoneum, lined by thickened and hyperplastic mesothelial cells. These proliferations occurred particularly in the regions of the fibrous adhesions, and they are undoubtedly the source of the cells that led to the confusion in examination of the sediment of the ascitic fluid, as Dr. Ackerman pointed out. I rather suspect that this situation is going to continue to be one of the most difficult pitfalls of clinical cytology. Individually these cells look very bad, and if a group of them are not called carcinoma none would ever be. On the other hand, whenever a positive diagnosis of carcinoma is made on ascitic fluid from a patient with long-standing ascites, it must always be kept in mind that in a certain percentage of such cases the cells will have arisen from hyperplastic mesothelium and not from a tumor.

The brain grossly was rather tight and soft. Figure 7 shows a section of the cerebral cortex. There are no focal lesions in the brain, but there are many large spaces about blood vessels and nerve cells. This is a treacherous criterion, but under conditions of fairly standardized fixation and histologic preparation excessive development of these spaces suggests the presence of edema. Many of the spaces are filled with the ghosts of neurons instead of the well stained cells typical of the cerebral cortex, and other spaces are filled with glial cells suggesting satellitosis and neuronophagia. These changes indicate extensive destruction of neurons throughout the cortex in addition to the edema. The pathologic picture is not specific. It is consistent with cases that have been diagnosed as hepatic coma and also with the diagnosis of myxedema of the brain. Figure 8 shows a section of the cerebellum in which there is an extensive loss of cells in the granular cortex. The Purkinje cells and glial cells on both sides of this layer of granular cortex are well preserved. It is strongly suspected that this change is at least in part artefact, but it seems to be quite extensive and suggests again an antemortem deterioration of neurons which may have been more susceptible to later rapid autolysis.

In summary, from the morphologic observations the diagnosis can be made of cirrhosis of the liver, and hyperplasia of the mesothelium of the peritoneum. The brain is interpreted as showing a non-specific picture of acute edema and death of cells which, at least statistically, is due more commonly to hepatic coma, although the alterations in the brain in myxedema and thyroid failure cannot be ruled out. In the thyroid there is evidence of fibrosis following therapy with radioactive iodine without positive evidence remaining of any previous hyperthyroidism.

DR. SCOTT: I wonder, Dr. Shank, if you would comment on the occurrence of hepatic coma in a patient in whom the non-protein nitrogen was only 18 mg. per cent.

DR. SHANK: That is distinctly unusual; I do not know that we have ever seen a definite case of hepatic coma without some increase in the non-protein nitrogen. One other point in regard to the liver function tests of importance here is that the serum cholesterol level was initially recorded as slightly over 100 and finally as 390 mg. One of the few alterations that is almost constantly associated with hepatic failure is a decrease in the total serum cholesterol. I have never seen a patient who died in hepatic coma in whom the serum cholesterol was as high as it was in this case. I would, therefore, like to suggest that although the changes in the brain were non-specific, the chemical evidence indicates that myxedema may have played a greater role in this patient's death than did hepatic failure.

Final anatomic diagnoses: Diffuse nodular cirrhosis of the liver; atrophy and fibrosis of the thyroid; edema and necrosis of neurons in the cerebral and cerebellar cortices.

Acknowledgment: Illustrations were made by the Department of Illustrations, Washington University School of Medicine.

Case Reports

Quinidine-induced Thrombocytopenic Purpura*

Report of a Fourteenth Case and Review of Clinical and Experimental Studies

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Brooklyn, New York

In view of the rarity of thrombocytopenic reactions to quinidine, it is the purpose of this report to present a fourteenth case which gave us the opportunity to study the pathogenic mechanism of this disorder and to review the clinical and experimental material presented in the literature.

The first report of thrombocytopenic purpura due to quinidine was made by Broch[1] in 1941. Since then twelve other cases have been reported.[2–12] Characteristically, bleeding manifestations occurred after the administration of quinidine and subsided following its discontinuance. The administration of a test dose of quinidine uniformly resulted in a precipitous fall of blood platelets and was frequently associated with bleeding manifestations. This sequence of events is suggestive of an anaphylactoid reaction, with platelets as the shock tissue. The *in vitro* platelet agglutination studies to be described corroborated the allergic etiology of this drug-induced thrombocytopenic purpura.

CASE REPORT†

A. W., a seventy year old white woman, was admitted to the Maimonides Hospital for the first time on December 16, 1952, because of diffuse ecchymoses of ten days' duration. She had had hypertension for five years. Three years previously she noted the onset of frequent episodes of supraventricular tachycardia and received quinidine intermittently, with improvement. One year prior to admission hematuria and scattered ecchymoses over the trunk and extremities developed. This appeared to be related to sulfonamide therapy taken for an upper respiratory infection rather than to quinidine. The bleeding gradually subsided during the next two weeks. One month prior to admission she developed erysipelas of the face and improved when given "biosulfa." Three days later (ten days prior to admission) the patient noted the sudden appearance of diffuse scattered ecchymoses and several hemorrhagic blisters on the tongue and buccal mucous membranes. One day prior to admission she passed several tarry stools.

The patient had been medicating herself with thiomeril for hypertension; aminophyllin, phenobarbital and papavarine for vague abdominal complaints; quinidine for supraventricular tachycardia; and sulfonamides for infections. These tablets were mixed in several bottles and judging from the patient's level of awareness she may have taken a particular drug without knowing it.

The patient's past history and review of symptoms were non-contributory.

Examination revealed the pulse rate to be 96 per minute; respirations 32 per minute; temperature 101°F. and blood pressure 150/50. The patient was a well developed, well nourished, elderly white female who appeared weak but not

† We are indebted to Drs. R. Janet Watson and Victor Groiser for referring this case to us for study and to Dr. Morris M. Banowitch, Acting Director of Medicine, Maimonides Hospital for granting us permission to report it.

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acutely ill. There was marked pallor of the skin and mucous membranes and diffusely scattered petechiae and ecchymoses were present over the trunk and extremities. There was a left periorbital hematoma and several hemorrhagic ulcers of the tongue and buccal mucous membranes. There was no icterus. The thyroid was symmetrically enlarged. On percussion the heart seemed to be slightly enlarged to the left. There was a soft blowing systolic murmur heard over the entire precordium. Numerous extrasystoles were present. The liver descended one finger-breadth below the right costal margin. There was no lymphadenopathy or splenomegaly.

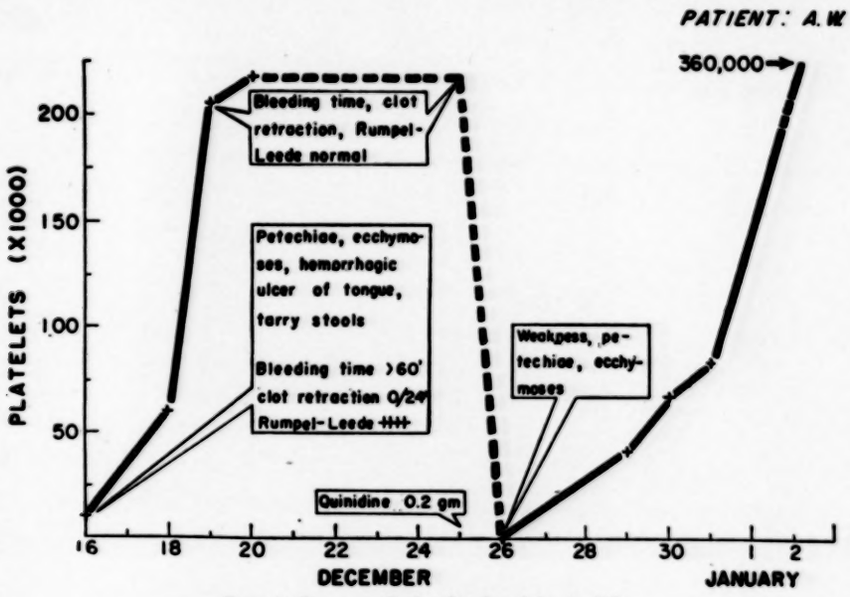


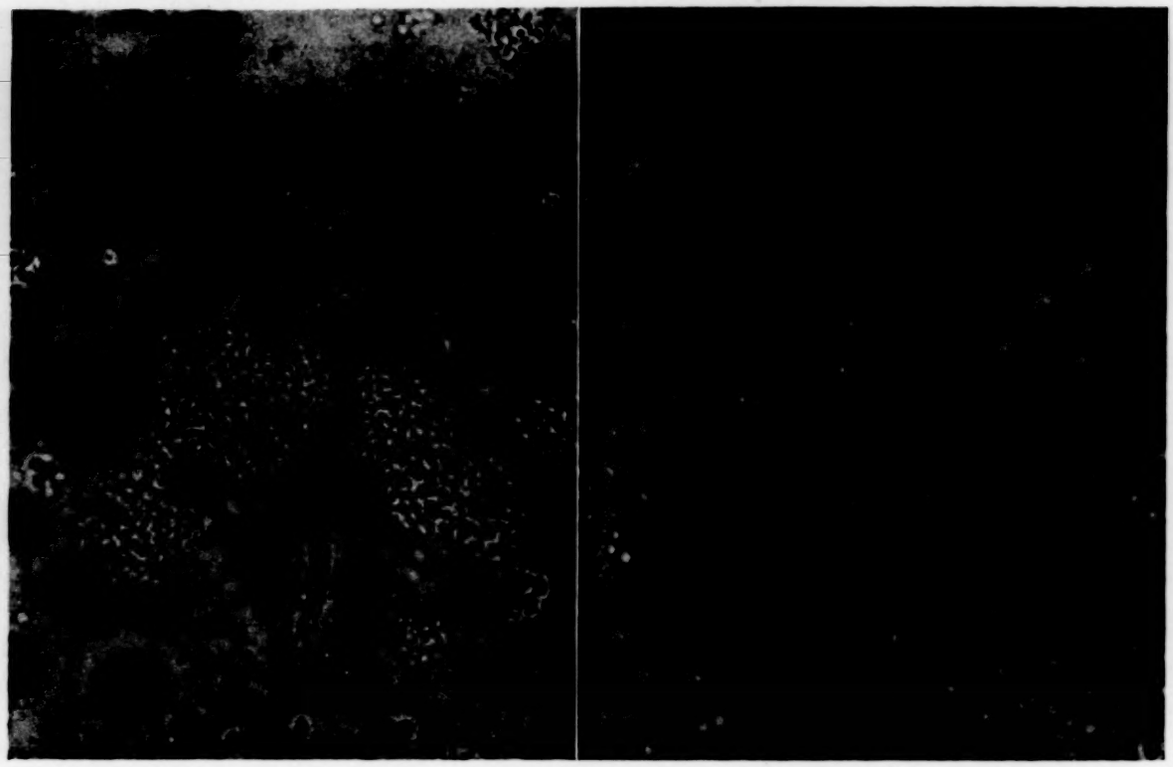
FIG. 1. Course of platelet level in A. W.

Laboratory data were as follows: Red blood cells, 2.75 m./cu. mm.; hemoglobin, 6.5 gm. per cent; mean corpuscular volume, 80.0/cu. micra; mean corpuscular hemoglobin, 24.0 gamma; mean corpuscular hemoglobin concentration, 25.0 per cent; white blood cells, 13,800/cu. mm.; reticulocytes, 4.5 per cent; platelets, 11,000/cu. mm.; coagulation time, seven minutes; Rumpel-Leede's test, markedly positive; bleeding time, more than sixty minutes; clot retraction, none in twenty-four hours; stool guaiac, 4 plus; Coombs' test—direct, positive; indirect, negative; cold agglutinins, negative; blood urea nitrogen, 24.0 mg. per cent; urinalysis, negative. The electrocardiogram revealed the presence of a supraventricular tachycardia.

The bone marrow was normally cellular. Megakaryocytes were reduced in number and those present were non-productive of platelets. There was moderate normoblastic hyperplasia. Granulopoiesis was orderly.

All drugs were discontinued although it was believed that the onset of the thrombocytopenic purpura was more specifically related to the recent sulfonamide therapy. One thousand cubic centimeters of blood were administered on admission. The platelet level rose rapidly so that on the fourth day it had returned to normal. (Fig. 1.) Bleeding time, clot retraction and Rumpel-Leede's test returned to normal. Petechiae and ecchymoses gradually subsided. The stools became guaiac-negative. On December 25, 1952, 0.2 gm. of "quinine" were ordered for a persistent arthritic complaint. The patient received, in error, 0.2 gm. of quinidine. Within twelve hours she complained of marked weakness and developed diffuse petechiae and ecchymoses over the entire body as well as the oral mucous membranes. Platelets were absent on the peripheral blood film. Bleeding time, clot retraction and Rumpel-Leede's test were markedly abnormal. With the discontinuance of quinidine platelets gradually rose to normal levels by the seventh day.

Blood studies performed on January 21, 1953, revealed the following: red blood cells, 3.9 m./cu. mm.; hemoglobin, 10.9 gm. per cent; reticulocytes, 1.2 per cent; white blood cells, 6,100/cu. mm.; differential: monocytes 8 per cent, lymphocytes 24 per cent, polymorphonuclears 64 per cent, bands 1 per cent, eosinophils 3 per cent. A repeat bone marrow aspiration ob-



2 3

FIG. 2. Intense platelet agglutination obtained upon incubation of patient's sensitized plasma, normal platelets and quinidine.

FIG. 3. Discrete platelet suspension obtained upon incubation of control plasma, normal platelets and quinidine.

tained on January 13, 1953, showed the presence of normal platelet-bearing megakaryocytes.

The patient has been examined repeatedly since then and has shown no recurrence of the bleeding phenomena.

Experimental Studies

Preparation of Test Plasma. Test plasma for *in vitro* agglutination studies were prepared by using sequestrene Na_2 as the anticoagulant, 0.3 ml. of a 5 per cent solution per 10 cc. of blood. The blood was centrifuged at 2,000 r.p.m. for fifteen minutes. The plasma was removed and stored at −20°C. until used. All plasmas were recentrifuged at 3,000 r.p.m. for fifteen minutes after thawing to remove all suspended materials.

Preparation of Platelet Suspensions. Platelet suspensions were prepared freshly on the day of use from 20 to 40 cc. of blood decalcified with sequestrene Na_2 as mentioned previously. Rigid silicone technic was employed in all platelet manipulation. The blood was centrifuged at 600 r.p.m. for twenty minutes and the platelet-rich supernatant was then removed as completely as possible without gross contamination by red cells. The plasma was then centrifuged rapidly three to four times in a table model angle centrifuge for one-minute intervals until maximum removal of red cells was effected. Very few platelets were sedimented by this technic. Only occasional red cells were seen in the low power microscopic field. The resultant platelet concentrations ranged between 300,000 to 600,000/cu. mm.

In Vitro Test Procedure. Test or control plasma, 0.1 ml., was added to 0.1 ml. of platelet suspension in siliconed tubes. The tubes were incubated at 37°C. for thirty minutes and then centrifuged at 500 r.p.m. for two minutes. Immediately before reading each tube was shaken by hand fifteen times to resuspend platelets. When quinidine was added to the system, 0.1 cc. of 15 mg. per cent quinidine solution was added to the solution, thus making a final concentration of 5 mg. per cent of quinidine.

Platelet agglutination was observed macroscopically. The degree of agglutination was recorded as 1 to 4 plus, depending on the intensity of clumping under both low and high powdered microscopic fields: i.e., 1 plus, ag-

glutination in small aggregates, visible only under high power field; 2 plus, agglutination just visible under low power field; 3 plus, moderate agglutination readily seen under low power field; 4 plus, intense agglutination easily seen under low power field.

trols" caused only sporadic agglutination of the platelet suspensions tested. None of these patients had any reduction in platelet level. Administration of quinidine to six normal individuals over a five-day period did not appear to stimulate the appearance of platelet aggluti-

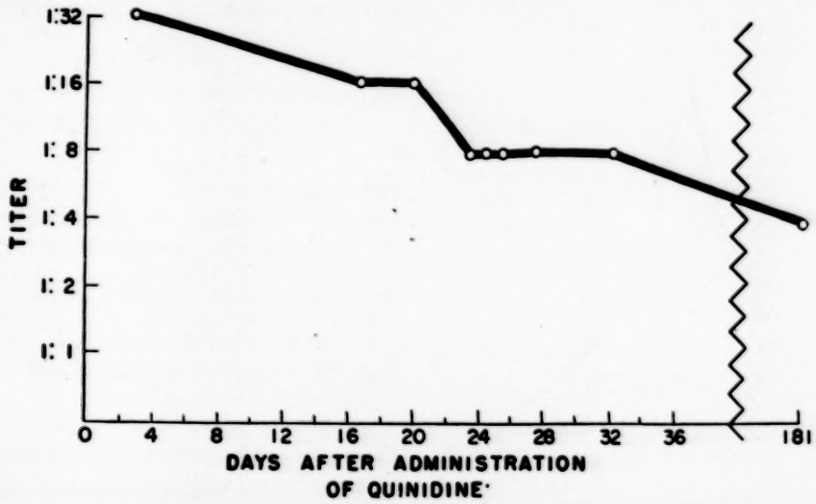


FIG. 4. Course of platelet agglutinin titers following the discontinuance of quinidine therapy in A. W.

No special precautions were taken to use compatible plasmas inasmuch as red cell clumping appeared to have no influence on the degree of platelet agglutination.

Demonstration of Platelet Agglutinins. Incubation of patient's or control plasma with platelet suspensions showed no agglutination, despite frequent intense red cell agglutination. The addition of quinidine to the system in the amount noted resulted in intense platelet agglutination by the patient's plasma (Fig. 2) whereas the control plasmas showed only discrete platelets. (Fig. 3.) Eighteen different platelet suspensions were used in these experiments. All showed marked agglutination when incubated with the patient's plasma and quinidine, thus indicating that the agglutinin is a panagglutinin for human platelets. The patient's own platelets were used, following their return to normal, in place of normal platelets. No agglutination resulted unless quinidine was added to the test system. Twenty different plasmas were utilized as controls. Seventeen of these failed to show any degree of platelet agglutination with quinidine included in the incubation mixture. Three plasmas, however, showed moderate degrees of agglutination. Upon further investigations of these donors it was found that they had a history of recent quinidine ingestion. Furthermore, these "controls" caused only sporadic agglutination of the platelet suspensions tested. None of these patients had any reduction in platelet level. Administration of quinidine to six normal individuals over a five-day period did not appear to stimulate the appearance of platelet agglutinins in their plasma when tested by the *in vitro* procedure outlined here.

Titration of Platelet Agglutinins. Plasma agglutinin titrations have been performed periodically since the recurrence of thrombocytopenia. The dilutions of the patient's plasma were made with normal sequestrenated plasma in order to avoid the use of saline. Figure 4 indicates the progressive reduction in agglutinin titer with time. Agglutinins, however, continue to be present at this writing, 181 days after the last dose of quinidine, though there is no current thrombocytopenia.

Role of Quinidine in the Agglutinin Reaction. Varying concentrations of quinidine were used in the incubation mixture. Figure 5 indicates the strength of platelet agglutination obtained. A final concentration of 5 mg. per cent of quinidine was found to produce maximum agglutination. Quinidine concentrations above and below this point were associated with suboptimal reactions. Concentrations below 0.33 mg. per cent were incapable of producing any reaction.

Quinine, the levorotary isomer of quinidine, was incubated in a concentration of 5.0 mg. per cent with the patient's plasma and normal platelets. No agglutination was noted, indicating the high degree of specificity of this reaction for quinidine.

Role of Platelets. As indicated, all human

platelets tested were agglutinated upon incubation with quinidine and the patient's plasma. Heterologous rabbit platelets could not be agglutinated by this system. Incubation of the patient's plasma and quinidine with homologous red cells showed no red cell agglutinating or lytic effects.

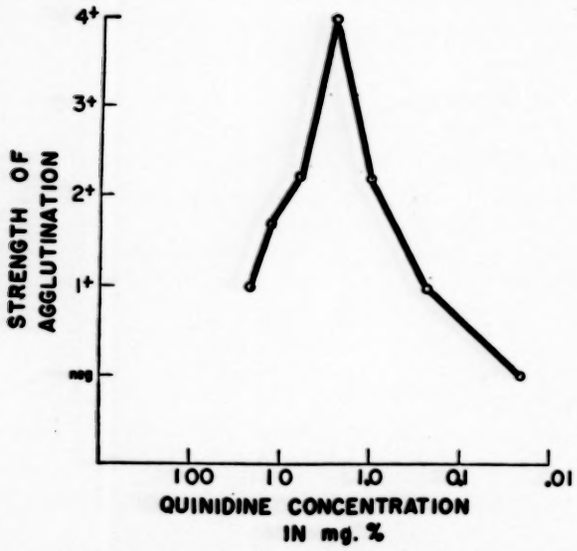


FIG. 5. Intensity of *in vitro* agglutination with varying concentrations of quinidine.

To determine whether a prior reaction between quinidine and platelets had occurred, these were incubated and the former removed by several saline washings. No agglutination resulted upon the addition of the patient's plasma to the washed platelets. This suggests the possibility that quinidine may act as an unbound intermediary between a plasma factor and platelets.

The agglutinin was completely absorbed from the plasma on to the platelets by several incubations of the same plasma with platelets from a uniform source.

Physical-Chemical Characteristics of the Platelet Agglutinin. The platelet agglutinin was equally active upon incubation at 4°, 25° and 37°C. Reduction of the period of incubation from thirty to five minutes produced equal intensities of agglutinations. Storage of plasma for two months at −20°C. failed to influence the degree of agglutination to any marked degree. Treatment of plasma with barium sulfate and tricalcium phosphate gel failed to affect the reaction.

Heating of the plasma for thirty minutes at 56° and 60°C. had no effect on the intensity of agglutination. At 65°C., however, there was complete loss of the plasma's ability to agglutinate platelets. Addition of guinea pig complement to inactivated as well as unaltered plasma failed to induce any platelet lysis. Half-saturation of plasma with ammonium sulfate resulted in a globulin fraction which agglutinated normal platelets in the presence of quinidine. The same fraction obtained from normal plasma failed to do so. The fractions of normal and patient's plasma soluble in 50 per cent saturated ammonium sulfate failed to affect normal platelets in the presence of quinidine. These results are summarized in Table I.

TABLE I
CHARACTERISTICS OF THE IN VITRO AGGLUTININ PRESENT IN QUINIDINE INDUCED THROMBOCYTOPENIC PURPURA

Treatment	Agglutination
Incubation at 4°C.	3+
Incubation at 25°C.	2–3+
Incubation at 37°C.	3–4+
Heating of plasma to 65°C.	Negative
Adsorption by barium sulfate or tricalcium phosphate	3–4+
Addition of guinea pig complement	4+
Optimal concentration of quinidine	5 mg. % (final)
Storage for 2 mo. at 20°C.	4+

REVIEW OF LITERATURE

The case reviewed herein brings the total number of reported cases of quinidine-induced thrombocytopenic purpura to fourteen Of these thirteen are females and one is a male. The age incidence varies from twenty-seven to seventy-six years, with the majority in the fifth and sixth decades. Five had paroxysmal auricular or supraventricular tachycardia; four had auricular fibrillation or flutter; and five were treated because of palpitation or other irregularities of the heart beat without benefit of electrocardiographic diagnosis.

Quinidine induced thrombocytopenia in six patients during their first course. The shortest interval of sensitization was four days in a patient who received a total of 6.4 gm. of quinidine. The smallest sensitizing dose was 4.4 gm. administered over a nine-day period. In three patients a second course was required to induce thrombocytopenia. In two of these the second course was given several months after initial treatment. In one patient 4.0 gm. of quinidine were ingested during the first course and 9.0 gm. during the second sensitizing course. Four patients received

intermittent quinidine treatment for periods varying from one to seven years.

The onset of purpura was preceded in some cases by weakness, epigastric distress, chills, fever and pruritus. (Table II.) Virtually all patients had petechiae and ecchymoses of the skin and a majority had bleeding of the gums. Epistaxis occurred in four patients and hematuria in two. Severe gastrointestinal bleeding was present in two patients who continued to take quinidine at the onset of purpura. Two patients showed ulcerative lesions of the mouth. Marked menorrhagia occurred in one patient menstruating at the time of sensitization to quinidine. Intracranial hemorrhage, suggested by headache, convulsions and coma, occurred in a sixty-six year old woman who had three previous episodes of spontaneous bruising and bleeding during the preceding seven years, each preceded by an attack of paroxysmal auricular fibrillation and quinidine therapy. The patient received 0.8 gm. within a one-hour period. Several hours later she had marked nausea, abdominal distress, weakness, petechiae of the skin and mucous membranes, epistaxis, hematuria, hematemesis, convulsions and coma.

The laboratory findings were invariably characteristic of thrombocytopenic purpura, i.e., poor clot retraction, prolonged bleeding time, positive Rumpel-Leede test, impaired prothrombin consumption and normal coagulation time (glass).

In three patients a peripheral eosinophilia of 6 to 10 per cent was noted. Bone marrow studies were reported in five cases. Megakaryocytes usually showed a smooth contour with diminished platelet production. In one instance the cytoplasm presented a glassy appearance. Good platelet production invariably followed discontinuance of quinidine. Active bleeding usually ceased within twenty-four hours following discontinuance of quinidine. Complete hematologic remissions occurred within periods varying from three to seventeen days. In seven patients this remission occurred within one week.

A test dose of quinidine, usually 0.2 gm. was administered to eleven patients. In all instances there was a precipitous fall in platelet level within a matter of hours. In seven patients there were rapidly developing hemorrhagic manifestations, including petechiae, ecchymoses and bleeding of the gums and epistaxis. In four patients there was moderate to severe thrombocytopenia without bleeding tendencies. These, as well as the hematologic abnormalities, rapidly returned to normal following discontinuance of quinidine. This test dose was of importance in our case inasmuch as the history suggested sulfonamides rather than quinidine as the etiologic factor.

TABLE II
CLINICAL MANIFESTATIONS OF THROMBOCYTOPENIC PURPURA INDUCED BY QUINIDINE

	No. of Cases
Premonitory symptoms:	
Weakness	4
Epigastric distress	2
Chills and fever	1
Pruritus	1
Hemorrhagic manifestations:	
Petechiae and ecchymoses	13
Bleeding of gums	8
Epistaxis	4
Hematuria	2
Gastrointestinal hemorrhage	2
Oral ulcers	2
Menorrhagia	1
Headache, convulsions, coma	1

Patch tests performed in two cases were negative. Intradermal skin test in one patient[3] resulted in a weak reaction. Substitution of quinine for quinidine resulted in a negative reaction. One attempt at desensitization was unsuccessful since hemorrhagic manifestations appeared when 0.03 gm. of quinidine was administered.

Investigations into the mechanism of quinidine induced thrombocytopenia were made by Bigelow and Desforges[10] and Larsen.[12] Platelet agglutinins were demonstrated by the former upon incubation of sensitized platelet-rich plasma with quinidine. Similar results were obtained upon the incubation of sensitized plasma with normal platelets and quinidine. Omission of quinidine from the test system uniformly resulted in negative agglutinations. The platelet agglutinin was still present twelve days after the cessation of quinidine therapy but absent on the thirty-ninth day. The agglutinin was quite active after storage at 20°C. for forty days. These investigators noted that serum was not as effective as plasma in inducing platelet agglutination.

Larsen,[12] utilizing clot retraction as an index of platelet activity, noted inhibition upon the addition of both sensitized serum and quinidine to normal whole blood. The optimal quinidine concentration was found to be 8 mg. per cent. The omission of sensitized serum or quinidine

from the test system resulted in normal clot retraction.

COMMENTS

Thrombocytopenic purpura has been reported to occur "secondary" to a large number of drugs, i.e., sedormid,® quinine, quinidine, gold, phenolphthalein, arsenobenzol, sulfanilamide, etc. It is characteristic of this type of thrombocytopenia that (1) the patient has received one of the aforementioned drugs either during a previous course or within the same course of treatment, (2) gradual improvement usually follows cessation of drug therapy (except in the case of gold due to its slow release from the tissues) and (3) readministration of the drug subsequent to a hemorrhagic episode will cause a prompt and severe reduction in blood platelets, frequently with bleeding manifestations. The marrow aspirate, an important aid in differentiating between primary and secondary thrombocytopenic purpuras, is usually indistinguishable in the drug-induced thrombocytopenias from that seen in the primary or idiopathic thrombocytopenic purpuras. In both groups the number of megakaryocytes is usually normal or increased, with diminished cytoplasmic granularity and diminished platelet productivity. Bone marrow eosinophilia may be noted in either type. In patients in whom an adequate drug or chemical history cannot be obtained, the marrow aspirate may be of no value in differentiating between idiopathic thrombocytopenic purpura and drug-induced (allergic type) thrombocytopenic purpura.

The behavior of blood platelets following readministration of an offending drug is strongly suggestive of a hypersensitivity phenomenon. Impetus to this concept came from the classical work of Ackroyd[13] on the pathogenesis of sedormid-induced thrombocytopenic purpura. The addition of sedormid to the blood of sensitized patients (following the return of platelets to normal) caused agglutination and lysis of platelets. Other studies revealed that sensitized serum, sedormid and normal platelets were the essential constituents of this reaction. Normal serum does not cause platelet agglutination or lysis. The omission of sedormid yielded negative results. Inactivated sensitized serum produced only agglutination of platelets upon incubation with sedormid. The addition of complement, however, resulted in platelet lysis. It was postulated that the combination of sedormid and platelets may be the antigen and that the presence of both is required for agglutination and lysis by the antibody.

The pathogenesis of quinidine-induced thrombocytopenic purpura has been studied by Bigelow and Desforges,[10] Larsen[12] and the present authors. It has been demonstrated that quinidine is an essential constituent of the reaction between sensitized patient's serum or plasma and normal platelets. In all probability quinidine itself is not antigenic. However, in combination with a serum protein and attached to platelets the resultant aggregate would be capable of antigenic stimulation. From our data, however, it appears that quinidine cannot be taken up firmly by platelets, since washing removes the quinidine and no agglutination occurs upon incubation with sensitized serum. It is of interest that the optimal concentration of quinidine in the test system is closely related to that present in the tissues following the ingestion of 0.2 gm. The high degree of specificity of this reaction is noted from the negative results obtained upon the substitution of quinine, a levorotary isomer of quinidine.

The agglutinin was found to be a panagglutinin reacting with all human platelets. Antibodies were found to be present within the patient's serum for at least 181 days following discontinuance of quinidine treatment, even though the thrombocytopenia had completely subsided. It is possible, therefore, that platelet destruction occurs only with very high antibody titers. Furthermore, the extreme rarity of this thrombocytopenic reaction to quinidine may be due to the fact that most individuals are poor antibody producers to quinidine-platelet stimulation. Sporadic agglutinins occurred in three of our normal controls who, upon further investigation, were found to have received quinidine recently. These reactions, however, were rather weak and could possibly be related to incompatibility of platelet type or to subclinical sensitivity to quinidine. The physical characteristics of the platelet agglutinin found in our patient are remarkably similar to those enumerated by Stefanini et al.[14] in his unusual patient with chronic idiopathic thrombocytopenic purpura.

Our studies have shown that, in contrast to the sedormid reaction, the antibody described possesses only agglutinating properties. The addition of guinea pig complement does not result in platelet lysis. The mechanism of platelet

destruction may therefore be due either to the increased mechanical fragility of platelet agglutinates as they are buffeted about in the circulation or to sequestration within the spleen.

Although there is marked reduction in megakaryocytic platelet productivity, this alone is insufficient to account for the tremendous rate of platelet loss. Both increased platelet destruction and diminished productivity appear to be responsible for the virtually total disappearance of circulating platelets within a matter of a few hours.

The recent contributions of Evans et al.,[15] Harrington et al.[16] and Stefanini et al.,[14] demonstrating the presence of platelet agglutinins in the serums of some patients with idiopathic thrombocytopenic purpura, has given considerable impetus to the immune concept of this disease. The recent investigations of sedormid-, quinidine- and quinine-induced thrombocytopenic purpura indicate that a similar pathogenetic mechanism is at work. The latter group has a good prognosis since removal of the offending agent is usually followed by complete remission. Although we do not have any clues as to the specific sensitivities which may be at play in idiopathic thrombocytopenic purpura, it is not inconceivable that such agents may be uncovered by future *in vitro* and *in vivo* investigations.

It is of great importance to prove the existence of a specific drug sensitivity, particularly when a variety of drugs has been recently administered. This was particularly true in our case since the history incriminated a drug other than quinidine. All investigators who have attempted the administration of a small test dose of quinidine have found this to be a relatively safe procedure and one which gave prompt and valuable information. It should be carried out under strict hospital supervision. *In vitro* testing, however, such as has been here described, may prove to be a more desirable means of detecting specific sensitizing drugs. It is entirely possible that other drugs or chemicals may produce similar *in vitro* reactions.

ACTH in one case[10] did not appear to accelerate the return of platelets beyond what would have occurred spontaneously following discontinuance of quinidine. Splenectomy has no place in the therapy of this or other types of drug-induced thrombocytopenic purpura since simple withdrawal of the offending agent results in complete remission.

SUMMARY

1. A fourteenth case of quinidine-induced thrombocytopenic purpura is presented.

2. An *in vitro* platelet agglutinin was demonstrated upon incubation of normal platelets, sensitized plasma and quinidine. Omission of quinidine from the test system uniformly resulted in a negative agglutination reaction. The antibody was found to be a panagglutinin since all human platelets so tested were agglutinated. Heterologous rabbit platelets could not be substituted for human platelets. Substitution of quinine, the levorotary isomer of quinidine, failed to produce any agglutination. The optimal concentration of quinidine was 5.0 mg. per cent. The role of quinidine is discussed.

3. The physical characteristics of this platelet agglutinin are described.

4. The importance of detecting specific sensitizing agents by *in vivo* and *in vitro* methods in determining the cause of the idiopathic or allergic types of thrombocytopenic purpura is discussed.

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Erratum: In Dr. W. Paul Haven's abstract published in our June 1953 issue and appearing on pages 902 to 904, the author wishes to call attention to a correction he deems important. On page 903, right hand column, the tenth line from the top should read: "(.500 mg./L.). It may be inactivated in plasma containing sulfa mustard (0.005 M final concentration) or beta-propiolactone (4 gm./L.)."

Erythrophagocytosis and Thrombocytopathy Occurring during the Course of a Henoch-Schönlein Syndrome Due to Quinine*

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THE physician's difficulties with the nosology, the pathogenesis and the clinical variations of the allergic purpuras were well set forth in a recent review by Ackroyd.[1] A general dichotomy of the allergic purpuras was offered: the Henoch-Schönlein syndrome and true purpura. The former was defined as purpura associated with an erythematous skin reaction and joint and visceral symptoms, all supposed to occur in response to a food allergy but without proof of that etiology to date. The latter group, the true purpuras, exhibits normal skin around the purpuric areas, and is known to be caused by a large number of drugs and infections. This group of purpuras may be associated with a low or normal platelet count and, occasionally, with demonstrable antibody activity against the formed elements of the blood.[2] Purpura of the Henoch-Schönlein syndrome is not associated with significant thrombocytopenia or, as far as has been known, with specific antibody attack upon platelets, red cells or white cells.

The purpose of this report is to describe a patient who, during the course of repeated Henoch-Schönlein episodes following quinine ingestion, also exhibited a number of immunohematologic phenomena. It is believed that this case may serve to relate the Henoch-Schönlein syndrome, in which antibody activity has been suspected but little documented,[3] a little more closely to certain immunohematologic disorders which have been rather clearly connected with specific antibody depredation.[4,5]

CASE REPORT

A twenty-eight year old male sergeant of Spanish-American extraction was hospitalized at Fitzsimons Army Hospital January 7, 1953, with moderately advanced tuberculosis of the right lung. On February 3, 1953, he was started on a regimen of bedrest, streptomycin and isonicotinic acid hydrazide. The regimen has been continued without change to date, with one exception which will be discussed. His tuberculosis has shown moderate clinical and x-ray improvement during the last ten months.

His family history was not contributory. His own past history and system review were not relevant, except that he contracted malaria in 1950 in Korea, and was treated with quinine. Also in 1950, while in Korea, he received shrapnel wounds of the back and left thigh. These healed well but left him with moderate atrophy of the left lower extremity, especially evident in the calf muscles.

In mid-May of 1953 he began to notice nocturnal cramps in the left lower extremity and a small, red, painful area in the arch of the left foot. At bedtime, on May 21st, he received 0.65 gm. of quinine sulfate for the cramping. On May 23rd, the red area on the arch of the left foot had ulcerated and was draining a small amount of purulent material. On May 24th a generalized, itching, erythematous rash appeared, with moderate swelling about the lips, feet and hands. By evening of that day, 1 to 3 mm. purpuric spots had appeared, mostly on the extensor surfaces of the extremities. His hypotrophic left leg had far more than its share of purpura and there was a 5 cm. area of ecchymosis about the lesion on the arch of the left foot. That same evening of May 24th he received his fourth and last oral bedtime dose of 0.65 gm. of quinine. That evening his temperature was

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FIG. 1. Swollen hands as they appeared after each of four quinine administrations. A fine, punctate erythematous rash was also visible at the bedside.

100°F., and he was given 300,000 units of procaine penicillin intramuscularly. On May 25th, the rash and itching increased, and all medications were stopped except nembutal® and benadryl®. On May 26th, his temperature was 103°F. and he was again given 300,000 units of procaine penicillin intramuscularly. It seemed to some observers that an additional erythematous rash with urticarial component was briefly superimposed on the preceding rash for the next twenty-four hours, after which the original purpuric and erythematous lesions were left to gradually fade over the next three days. Generalized desquamation of the skin followed for many days. On June 3rd, isonicotinic acid hydrazide was resumed without untoward reaction, and on June 8th, streptomycin was resumed also without untoward reaction. It was then suggested that the only likely candidate left to indict for his Henoch-Schönlein type of reaction was quinine.

Accordingly, on July 2nd, at 9 A.M., he was given 0.016 gm. of quinine sulfate by mouth. At 11 A.M. of that day he exhibited swollen hands and feet, and complained of stiffness of all his joints. The hands were especially swollen and red. (Fig. 1.) His lips were stiff and nearly twice normal size. He complained of generalized itching of the skin which showed a fine, punctate redness, without obvious purpura. His temperature was 99°F. By evening he was much improved. He had not complained of real joint pains, only stiffness, and no abdominal pain, only anorexia. On July 3rd, he felt well and for the next seven days suffered only mild desquamation of the skin.

On August 12th, at 8:30 A.M., he received 0.016 gm. of quinine sulfate by mouth again. By 11 A.M., swelling of the small joints, puffiness of the face and the fine, punctate, erythematous rash without obvious purpura had appeared. In twenty-four hours he was again free of symptoms except for desquamation.

On November 4th, he received 0.032 gm. of quinine sulfate by mouth at 8 A.M. The same symptoms and signs appeared at the same interval as on the previous three occasions, although this time they were less severe than before.

The significant laboratory aberrations that appeared during the six months we observed this patient were: erythrophagocytosis, a serum factor that could induce erythrophagocytosis in normal blood, eosinophilia, increased capillary fragility, morphologically abnormal platelets, possible platelet phagocytosis, abnormal clot retraction and mild, transient thrombocytopenia. These data, correlated with clinical status and drug administration, are shown in Table I.

Laboratory Methods. Red cell counts, white cell counts, red cell fragility, hematocrits, platelet counts, clot retraction observations, capillary fragility, Coombs tests, isoagglutinin titrations, bleeding times, coagulation times, reticulocyte counts, urine examinations, heterophile agglutinin, Wassermann, routine agglutinins, and bone marrow examinations were all performed according to well recognized, routine methods.

Erythrophagocytosis was sought by inspecting the patient's buffy coat prepared as follows: 5 cc. of venous blood were drawn from the patient and coagulation prevented with 0.1 cc. of 10 per cent disodium versenate. The specimen was incubated in the water bath at 37°C. for one hour. It was then centrifuged at 2,000 rpm for fifteen minutes. Most of the plasma was withdrawn and discarded, and the uppermost cubic centimeter of the remaining contents of the tube was transferred to a Wintrobe tube. This was then centrifuged at 3,000 rpm for twenty minutes. A buffy coat of several millimeters resulted from this double concentration method which yielded very rich smears of white cells. These smears were stained with Wright's stain and inspected under the oil immersion objective of the microscope.

TABLE 1

LABORATORY DATA

Drug Administration	Immediate Rash and Edema	Purpura	E.P. in Buffy Coat	Platelet Count	Clot Retraction	Platelet Morphology	Skin Tests	Eosinophil Count (%)	Serum Transfer of E.P.	Specific Thrombocytolysis	Coombs Test (direct)	Coombs Test (indirect)	Isoagglutinin Titer	Capillary Fragility	Bleeding Time	Coagulation Time
1st quinine administration, May 21–24; 2.6 gm.:	+++	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–
May 25	+++	++	–	317,000	Nor.	–	–	7	–	–	–	–	–	++	2 min.	6 min.
May 26	+++	++	–	166,000	Nor.	–	–	–	–	–	–	–	–	–	–	–
May 27*	+++	++	–	206,000	–	–	–	–	–	–	–	–	–	–	–	–
May 30	±	±	–	–	–	–	–	–	–	–	–	–	–	–	–	–
June 8	–	–	–	–	–	–	–	7	–	–	–	–	–	Neg.	–	–
June 10	–	–	–	–	–	–	Quinine SM. INH Neg.	–	–	–	–	–	–	–	–	–
July 1	–	–	–	144,000	–	–	–	9	–	–	–	–	–	–	–	–
2nd quinine administration, July 2, 9 A.M.; 0.016 gm.:	–	–	–	112,000	–	–	–	–	–	–	–	–	–	–	–	–
July 2, 11 A.M.	+++	–	–	84,000	–	–	–	–	–	–	–	–	–	Neg.	–	–
July 3*	±	–	59%	146,000	–	Nor.	–	4	–	–	Neg.	Neg.	Hemol. Neg.	–	–	–
July 10	–	–	–	–	–	Nor.	–	–	80%	–	–	–	–	–	–	–
July 20	–	–	10%	–	–	–	–	–	–	–	Neg.	Neg.	Hemol. + 1:4	–	–	–
July 23	–	–	Neg.	–	–	Nor.	–	–	Neg.	–	–	–	–	–	–	–
Aug. 3	–	–	Neg.	–	–	Nor.	–	–	Neg.	–	–	–	–	–	–	–
Aug. 5	–	–	–	–	–	–	–	–	–	Neg.	–	–	–	–	–	–
Aug. 11	–	–	Neg.	178,000	–	–	–	1	Neg.	–	–	–	–	–	–	–
3rd quinine administration, Aug. 12, 8:30 A.M.; 0.016 gm. at 11:00 A.M.:	++	–	Neg.	108,000	–	±	–	3	Neg.	–	Neg.	–	–	–	–	–
Aug. 13†	±	–	Neg.	–	–	±	–	–	Neg.	–	–	–	–	–	–	–
Aug. 14	–	–	Neg.	–	–	+	–	–	Neg.	–	–	–	–	–	–	–
Aug. 17	–	–	Neg.	–	–	+	–	–	Neg.	–	–	–	–	–	–	–
Aug. 21	–	–	Neg.	–	–	Nor.	–	–	Neg.	–	–	–	–	–	–	–
4th quinine administration, Nov. 4, 9 A.M.; 0.032 gm. at 11:00 A.M.:	++	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Nov. 6	–	–	Neg.	90,000	–	+	–	–	Neg.	–	–	–	–	–	–	–
Nov. 7	–	–	Neg.	–	–	++	–	–	Neg.	–	–	–	–	–	–	–
Nov. 9	–	–	Neg.	124,000	–	++	–	–	Neg.	–	–	–	–	–	–	–
Nov. 10	–	–	Neg.	–	–	–	–	–	Neg.	–	–	–	–	–	–	–
Nov. 12	–	–	Neg.	–	–	+++	–	–	Neg.	–	–	–	–	–	–	–
Nov. 17	–	–	–	–	–	++	Quinine Neg.	–	–	–	–	–	–	–	–	–
Nov. 19	–	–	–	–	81% Nor.	+	–	–	–	–	–	–	–	–	–	–
Nov. 30	–	–	3%	–	86% Nor.	+	–	–	Neg.	–	–	–	–	–	–	–
Dec. 8	–	–	–	–	56% Nor.	±	–	–	–	–	–	–	–	–	–	–
Dec. 17	–	–	–	–	150% Nor.	Neg.	–	–	–	–	–	–	–	–	–	–
Dec. 21	–	–	–	–	117% Nor.	Neg.	–	–	–	–	–	–	–	–	–	–
Dec. 28	–	–	Neg.	–	–	–	–	–	Neg.	–	–	–	–	–	–	–

* Heterophile, Wassermann, routine agglutinin tests, bone marrow all normal.

† Red cell fragility in hypotonic saline normal.

Note: Repeated WBC, PCV, urine examinations and reticulocyte counts remained normal throughout the course of this study.

Erythrophagocytosis was induced when the serum of the patient was allowed to act upon normal blood cells in the following manner: 1 cc. of packed, thrice-washed, normal, compatible red and white cells was added to 1 cc. of the donor's serum. This mixture was allowed to stand at 37°c. for thirty minutes and then the supernatant serum was withdrawn and discarded. The residual material was then centrifuged in a Wintrobe tube for twenty minutes at 3,000 rpm and the buffy coat smeared, stained and inspected as described.

Specific thrombocytolysis, requiring interaction of quinine, platelets, complement and the patient's serum, was sought according to the methods of Grandjean[6] and Ackroyd.[7]

Clot retraction was studied semi-quantitatively in the following manner: exactly 5 cc. of the patient's venous blood was placed in a graduated, conical centrifuge tube; the top was stoppered with a cork through which were inserted two copper wires coarsely braided together. These wires reached to the bottom of the tube and aided in the later withdrawal of the clot. The blood was allowed to clot at room temperature, and was then placed in a 37°c. water bath for one hour. After the hour's incubation the clots were withdrawn and the residual serum volume recorded. The tubes were then centrifuged at 3,000 rpm for twenty minutes, and the volume of the free red cells that had formed into a button was subtracted from the expressed serum volume. Normal controls were prepared in identical fashion. The expected expressed serum volume of the patient, calculated by proportion from the values obtained from the normal controls and corrected for differences in hematocrit, was then derived, and the actual expressed serum volume of the patient stated as a percentage of the expected figure. There was sufficient agreement in values among the several normal controls used to indicate that the patient's diminution in clot retraction was undoubtedly real.

Results. Table 1 is a compendium of laboratory findings as they were associated in time with the clinical observations.

Each of the four separate administrations of quinine was followed in several hours by a Henoch-Schönlein type of reaction. It should be noted that definite purpura followed only the prolonged administration of quinine sulfate in May. Subsequent administrations in July, August and November were only single doses of 16 or 32 mg. Figure 1, from the July 2nd episode, is a fair reproduction of the red, swollen hands of the patient as they appeared after each of the four administrations of quinine.

Certain difficulties were encountered in studying this patient. He was understandably averse to taking quinine after his initial episode and could only be persuaded to take fractions of a tablet at a time. In addition, each venipuncture was the fruit of considerable tact and diplomacy. Most hampering of all was the intermittent appearance of the laboratory phenomena, plus the contamination of one crucial batch of serum, so that many desirable determinations could not be performed. Nevertheless we are able to present a considerable array of apparently immunohematologic abnormalities that occurred in this patient in fairly good temporal relation to the administration of quinine and to the immediate Henoch-Schönlein effect of that drug.

Erythrophagocytosis was not seen in ordinary peripheral blood smears taken during the May episode. However, buffy coat preparations were not made at that time and a few erythrophages could have been missed. Twenty-four hours after the July administration of 16 mg. of quinine sulfate, 59 per cent of all the patient's circulating phagocytes were found to be ingesting one to four red cells each. (Fig. 2.) This phenomenon diminished over about three weeks and was never seen again despite two more quinine administrations. A small number of erythrophages were seen on November 30th, not in clear temporal relationship to any administration of the drug. The significance of this isolated finding is doubtful.

When erythrophagocytosis was at its peak in the patient's blood, his serum exhibited a powerful ability to induce erythrophagocytosis in normal blood. (Fig. 3.) Limited experiments demonstrated that this serum factor did not require complement for its activity, and that it could be removed from the serum by absorption with red cells; however, a short serum supply prevented us from adequate repetition and confirmation of these last two observations.

Appreciable but not profound drops in platelet count can be noted on May 26th, July 2nd, August 12th and November 6th, all of these times being immediately after quinine administration.

Clot retraction was normal during the May episode and was not tested in July or August, but with the appearance of platelets with grossly

FIG. 2. Erythrophagocytosis, as seen in the patient's blood, July 3rd; × 2,500.

FIG. 3. Erythrophagocytosis induced by the action of the patient's serum on normal blood. (Note eosinophil ingesting a red cell at upper left); × 2,500.

abnormal morphologic features in November (Fig. 4), clot retraction studies by the method indicated demonstrated diminished retractility. (Table I.)

The abnormal platelet morphology noted under date of August was minimal, and only discerned in retrospect after the grossly abnormal forms were seen in November.

Only one attempt was made at searching for specific thrombocytolysis, on August 5th, after the third quinine administration. Such an activity was not demonstrated.

Figure 5 shows one polymorphonuclear cell that appears to be phagocytizing a platelet. Many such forms were seen when erythrophagocytosis was at its peak, and we are inclined to believe that phagocytosis of platelets, in exact analogy to phagocytosis of red cells, was in progress. But owing to the small size of the platelet and the ease with which it can overlie any object on a blood smear, we cannot regard platelet phagocytosis as proved here. Microcinematography would probably be the proper way to establish this phenomenon firmly.

COMMENTS

Specific antibody activity against red cells, white cells and platelets may occur as separate

FIG. 4. Abnormal platelets of November 12th; (buffy coat preparation); × 1,250.

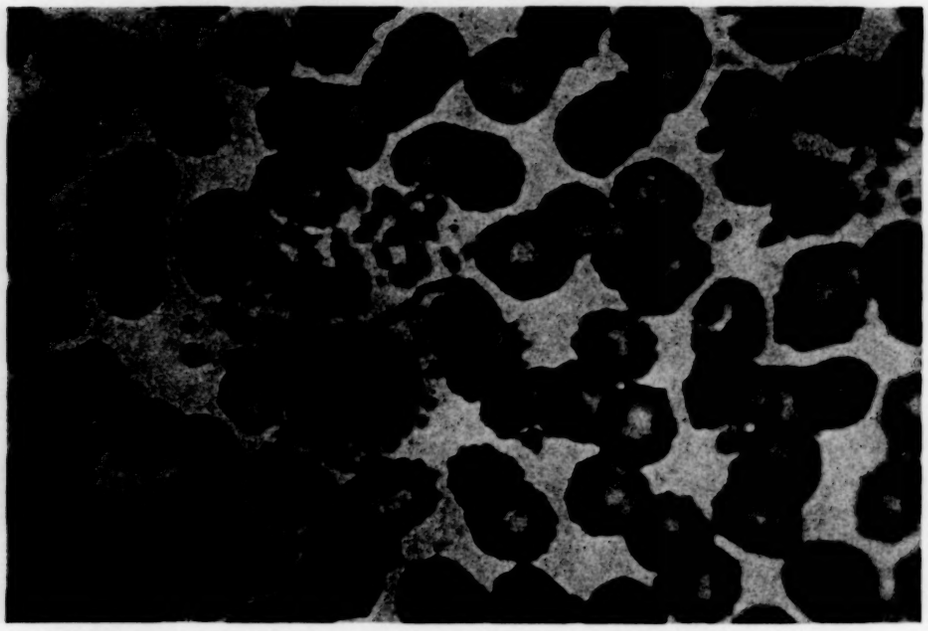

FIG. 5. Polymorphonuclear cell possibly exhibiting platelet phagocytosis, July 3rd; × 3,000.

bisease entities such as acquired hemolytic anemia or idiopathic thrombopenic purpura,[4,5] or during the course of such disorders as lupus erythematosus disseminatus[2] or periarteritis nodosa[8] as a subsidiary complication of the primary disorder. It is an impressive epidemiologic observation that these complications involving demonstrable antibody activity against the formed elements of the blood occur largely among a group of diseases in which hypersensitivity is thought to play a major pathogenetic role. It is not an unnatural supposition

that if antibodies can be shown to attack tissues easily available for separate study, then antibodies may very well also be responsible for disorders of tissues not so easily available for study. Thus, if the hemolytic anemia in a case of lupus erythematosus disseminatus can be shown to be due to antibody activity, then the renal, joint and vascular disease present at the same time might well be due to antibody activity also, although the proof is admittedly difficult to obtain.

While these remarks are not entirely out of order with regard to lupus erythematosus disseminatus, periarteritis nodosa, rheumatic fever, glomerulonephritis and some other related disorders, there is little reason to date to apply them to the Henoch-Schönlein syndrome, which has long been classified as an allergic affliction. It was, therefore, with considerable interest that we observed after each of four administrations of quinine in our patient a Henoch-Schönlein syndrome, complicated by both red cell and platelet disorders.

Erythrophagocytosis of prominent degree was seen in the patient's peripheral blood following the first test dose of quinine. This persisted for three weeks, and at the same time the patient's serum exhibited a strong ability to induce erythrophagocytosis in normal blood. One may therefore presume that we were dealing with an anti-red cell antibody, although it was not of the kind which gives the usual positive, direct Coombs test. It is puzzling that the patient did not develop anemia at this time in view of the fact that three-fifths of his phagocytes were busily engaged in engulfing red cells. Whether the erythrophagocytosis was too short-lived in its florid state to produce anemia, or he easily and completely made up for increased destruction by increased production is not known. One also wonders why erythrophagocytosis did not appear after the two subsequent administrations of quinine. Had a "refractory state" supervened? A delay of almost three months between the third and fourth administrations of the drug was deliberately planned in order to allow for this possibility. If we had given the patient several grams of quinine over several days, might we have induced erythrophagocytosis again? It is possible that such an intensive course of administration was necessary, as emphasized by Ackroyd,[1] but it was quite impossible to obtain our patient's consent to taking large doses of the drug.

Erythrophagocytosis has received considerable attention lately as a prominent phenomenon of hemolytic anemia. Wasastjerna regards it as one of the three principal causes of red cell destruction, along with buffeting of the circulation and antibody activity *per se*.[9] Zinkham and Diamond tabulated many settings in which erythrophagocytosis had been prominent, from naphthalene and potassium chlorate poisonings to acquired hemolytic anemia; in the latter disorder they thought erythrophagocytosis a valuable diagnostic sign.[10] Erythrophagocytosis has also been described in dogs after bilateral nephrectomy,[11] after irradiation,[12] when red cells were treated with Newcastle disease virus,[13] in lupus erythematosus disseminatus,[14] in advanced, bilateral renal disease,[32] in plasma cell leukemia,[15] in eclamptogenic toxemia of pregnancy[16] and during the production of nucleophagocytosis by rabbit antileukocytic serum.[17] It may also be noted that erythrophagocytosis is occasionally seen in tuberculosis.[10,18] It is true that our patient was tuberculous but the sharp correlation in time between quinine administration and the erythrophagocytosis he exhibited for just three weeks makes it seem unlikely to us that tuberculosis was the sole setting for the erythrophagocytosis seen.

It does not appear clearly set forth in the literature that erythrophagocytosis may be induced in normal blood *in vitro* by the addition of serum from a patient exhibiting erythrophagocytosis. This was easily accomplished in our case to the extent that 80 per cent of the normal phagocytes were ingesting red cells. Obviously such behavior is analogous to the kind of serum-borne anti-red cell antibody activity seen in Rh disease and acquired hemolytic anemia, as demonstrated by the indirect Coombs test.

The patient exhibited undoubted increased capillary permeability (as judged by the cuff method) only once, after the first dose of quinine. This was the only instance of obvious purpura too. Both of these phenomena might have reappeared had intensive quinine administration been possible.

A number of abnormalities were exhibited by the platelets during the patient's Henoch-Schönlein episodes following quinine. First, there were transient, mild decreases in number. One might presume this was accomplished by agglutination and/or lysis such as in the instance due to quinine described by Grandjean,[6] or as in the

cases due to sedormid elucidated by Ackroyd.[7] However, we were unable to discover such a system in operation in our case, there being no platelet agglutination or lysis *in vitro* upon the addition of complement, quinine and our patient's serum.

Platelet phagocytosis appeared to be prominent when erythrophagocytosis was at its peak; but, as has been mentioned, we do not regard fixed preparations as final proof of this phenomenon. The possibility of platelet phagocytosis as a major cause of platelet destruction, in direct analogy to red cell phagocytosis, has received remarkably little attention. Dameshek has given the topic some notice,[19] as has Tocantins,[20] but platelet phagocytosis in immunothrombocytopenia and related disorders has not received the particular study that it may deserve.

Bizarre macroplatelets such as were seen in our patient are well known to appear in periods of rapid platelet regeneration.[20] Tocantins also states that macroplatelets appear in three or four hours after intraperitoneal injections of antiplatelet serum in dogs.[20] It is not clear why macroplatelets were not at least as constant in their appearance in our patient as the occurrence of platelet diminution after each quinine administration. However, the impression remains that the macroplatelets seen are suggestive of platelet destruction of immunologic nature.

The diminution in clot retracting ability that appeared after the November quinine administration, and the major shower of macroplatelets, seems scarcely to be due to the modest decrease in platelets numbers alone. One wonders if an immunologic insult to platelets can result in diminished clot retracing ability even though the platelet numbers remain near normal. Our studies provide no support for such a suggestion beyond the general setting in which the phenomenon occurred. In this connection, a report of several cases of "partial platelet dysfunction" is of interest.[21]

The Henoch-Schönlein syndrome is most frequently associated with a certain food as the offender, and hence its repeated appearance following drug therapy in this case is distinctly unusual.[1] Quinine administration has, of course, often been followed by thrombocytopenic[22] and athrombocytopenic purpura[22,23] and by acute hemolytic anemia,[24] but we are not aware of ingestion of the drug being followed by a Henoch-Schönlein type of response, together with erythrophagocytosis and certain platelet abnormalities. Many drugs cause disorders of the formed elements of the blood. Thus, hemolytic anemia, a leukemoid reaction and purpura have followed the use of sulfapyridine;[25] thrombocytopenia, purpura, granulopenia and anemia, the use of dinitrophenol;[25] thrombocytopenic purpura and granulopenia that of gold;[27] and granulopenia and thrombopenia that of thiourea.[28] Specific reagins have been found to salvarsan, formaldehyde, phthalic anhydride, chloramine-T, sulfathiazole and sulfadiazine,[29] but the interrelationships of a specific drug, the antibody it may engender and the tissue of impact are not well worked out within the province of a single specific agent and host. Grandjean's report of quinine thrombocytolysis[6] and Ackroyd's elucidation of sedormid thrombocytolysis[7] are possible exceptions. It is known that quinine is taken up by endothelial cells, and that the drug increases amboceptor hemolysis of red cells *in vivo*.[30] One might consider these last observations as support for the postulate that quinine is capable of forming derivative antigens in combination with certain tissues. The facets of the syndrome that result from ingestion would then depend upon the number of different derivative antigens formed, as well as the ability of the particular host to manufacture antibodies.[31] In the case here presented we have had to rest content with the circumstantial thesis that coeval immunohematologic abnormalities suggest that the Henoch-Schönlein episodes had an analogous pathogenesis.

SUMMARY

A patient is presented who exhibited a Henoch-Schönlein type of response after each of four administrations of quinine.

At various times during these four episodes a number of typically immuno-hematologic disorders appeared: erythrophagocytosis, a serum factor that could induce erythrophagocytosis in normal blood, increased capillary fragility, transient diminution in numbers of platelets, abnormal platelet morphology, possible phagocytosis of platelets and decreased clot retraction.

It is suggested that the occurrence of such immunohematologic phenomena, well known in other contexts to be due to specific antibody behavior, lends support to the contention that the Henoch-Schönlein syndrome is an example of antibody depredation upon tissues. The occurrence of erythrophagocytosis, induced by the activity of the patient's serum on normal blood,

is especially strong associational evidence for this point of view.

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Primary Carcinoma of the Liver with Early Metastasis to the Spine and Initial Symptoms of Paraplegia*

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PRIMARY carcinoma of the liver may arise from liver cells (malignant hepatoma), intrahepatic bile duct cells (malignant cholangioma), or both (mixed type). Primary malignancies of the liver are most common in the Bantu natives of South Africa, a tribe whose diet is markedly deficient in proteins and vitamins. They are also common among the peoples of Asia, especially India, Malaya, China and Japan.[1] In Europe and this country primary carcinoma of the liver is less common, although there is some evidence that it is increasing in frequency.[2-4] In 1947 a review of the literature reported 339 cases in 159,144 necropsies of North Americans and Europeans,[5] an incidence of 0.227 per cent. A more recent review[6] compiled a total of 1,391 cases, presumably including those reported from Africa and the Orient.

The diagnosis is difficult to establish before autopsy. When made antemortem it is usually predicated on a rapid downhill course in a patient known to have cirrhosis of the liver, with confirmation from surgical or needle biopsy of the liver. The disease is usually rapidly fatal although survival for periods as long as four to six years has been reported.[3] Metastatic lesions are of varying incidence in different reports. Metastasis to bone is said to occur rarely.[6] When it does occur, the spine is a site of predilection.[5] A review of the available literature did not disclose a case with course and presenting symptoms similar to the one to be described.

CASE REPORT

G. W. K., a fifty-nine year old white male farmer, became ill in March, 1952, with rather severe pain in the posterior cervical region, radiating into both shoulders. This difficulty was followed by motor weakness of the extremities progressing to inability to stand or to move the lower extremities. On physical examination the patient was a well developed, poorly nourished, chronically ill man with normal temperature, pulse and blood pressure. He was found to have a paralysis from the level of T-2 downward, with spasticity of the muscles of the lower extremities. There was anesthesia below T-2 except for vibratory sensibility which extended down to T-4. The deep reflexes were hyperactive. The Babinski reflex was positive bilaterally and there was a bilateral sustained ankle clonus. Atrophy of the interosseus muscles of the hands was present as well as less marked atrophy of the muscles of the arms and forearms. The blood counts, urinalyses and the blood serologic tests were within normal limits. X-rays of the skull, spine and pelvis revealed a lesion of bone destruction in the spine extending from C-7 to T-2. The cerebrospinal fluid had a low pressure with no increase on jugular compression and was xanthochromic in appearance. It contained 2 lymphocytes per cu. mm., the proteins were elevated to 200 mg. per cent, the spinal fluid serology was negative and the colloidal gold curve was 0001110000.

The patient was transferred to a hospital specializing in the study of neoplastic diseases where a myelogram showed obstruction at the level of T-2. An exploratory operation revealed a firm, encapsulated, yellowish mass adjacent to the spine of T-2, posterior to its lamina. Dissection revealed that the entire left lamina of T-1 was eroded and a part of the mass occupied the extradural space at that level. The mass was resected down to the extradural space. The report of a frozen section was that of metastatic carcinoma, probably of renal origin. It was considered unwise to do an extensive laminec-

* From the Veterans Administration Hospital, Tuscaloosa, Ala.

tomy and the wound was closed. Fixed sections of the mass showed "metastatic malignant tumor with a fibrous stroma and a glandular structure seen in both longitudinal patterns and acini. There is much variation in cell size. Syncytial groupings resembling foreign-body giant cells are seen." The patient was returned to our hospital for terminal care. He was paraplegic and it was necessary to maintain an indwelling catheter. Morphine sulphate in increasing doses was necessary for the relief of pain in the shoulders. Examination of the patient was difficult as he had strong reflex muscular spasms when touched about the body or extremities. Antibiotics of various sorts were given for control of urinary infection. On March 26, 1953, he was found to have mild edema of the abdominal wall and moderate edema of the legs. "Liver" palms were noted at this time. The abdomen appeared distended but no masses or organs could be palpated, possibly due to the reflex muscle spasm. Mercuhydrin® was administered with some decrease in the edema. One week later he complained of dyspnea. He was digitalized on an empiric basis with some relief. On April 21, 1953, the temperature rose to 105°F. On the following day many moist rales were noted over the lung fields and the skin of the back was edematous. More mercuhydrin was administered. His condition steadily deteriorated, with development of anorexia, air hunger and anxiety. The fever continued. The patient lapsed into coma and died quietly on April 27, 1953, after thirteen months of illness.

Positive findings at autopsy included a liver which weighed 3.15 kg. It was estimated that 80 per cent of the substance of the right lobe consisted of tumor tissue. Ninety-nine per cent of the left lobe was normal tissue with the remaining 1 per cent being in the form of small, discrete, grayish white, button-like nodules beneath the capsule. These measured up to 15 mm. in diameter. A tumor mass lay in the right lobe beneath the diaphragm and measured 10 by 9 cm. in length. It was hard and the cross sections were white. Spreading from it the remainder of the right lobe was riddled with heavy bars and nodules of tumor tissue. Branches of the portal vein were occluded in the tumor mass and the parenchyma surrounding the masses was grossly compressed. As the tissues overlying the spine were dissected, the tissue became tense, firm and gray-white. Black thread sutures were encountered. The vertebral processes were removed by snipping with heavy shears and a cord segment 7 cm. long was removed. This represented the cervical enlargement and a portion of the upper thoracic segment. The dura was thickened and appeared gray-white. Cross section of the cord revealed moderate loss of the finer anatomic details. The kidneys were normal except for pyonephritis, more marked on the left No other metastatic lesions were found.

Several sections of the liver tumor were examined and in nearly all areas it presented a similar and uniform architecture. It was characterized by cell clusters surrounded by thick mantles of connective tissue. Among the clusters of tumor cells were forms which appeared atrophic and in varying stages of degeneration while there were other clusters that showed remarkable variation in cell size and staining quality. In some areas the cells appeared quite large and polyhedral and at times aligned themselves to form a duct or gland-like structure. Frequently, vacuoles containing pink-staining bodies were seen. These varied considerably in size. The nuclei of the tumor cells tended to be large and vesicular although the chromatin particles were coarse. Enormous nucleoli were within the nuclei and they assumed a variation of shapes.

Several sections were made at varying levels of the segment of spinal cord removed at autopsy. None of the sections showed tumor cells. All showed extreme grades of degeneration. There was a marked alteration of structure in the region of the spinal tracts. Extremely large vacuoles were present in these areas. Corpora amylacea were numerous and often clustered. The neurons of the gray matter were markedly shrunken, distorted and had smudge-like staining qualities. Fragments of partly destroyed neurons remained. Many were missing. No other tumor was found in the body. The microscopic sections were reviewed by the Armed Forces Institute of Pathology with confirmation of the diagnosis of primary malignancy of the liver (malignant cholangioma).

COMMENTS

The case which forms the basis for this report is an unusual instance of primary carcinoma of the liver with paraplegia as the presenting symptom. While postmortem examination did not reveal tumor cells in the cord, the surgical biopsy report—in the absence of any other type of tumor at autopsy—is regarded as furnishing

convincing evidence that the paraplegia was due to pressure on the spinal cord at the level of T_2 from a solitary metastasis to the spine which arose from a malignant cholangioma.

SUMMARY

A case of primary carcinoma of the liver with presenting symptoms of paraplegia is described.

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[1]Sturnick, M. I., and Gargill, S. L.: Clinical Assay of a New Synthetic Estrogen: Vallestril, New England J. Med. *247*:829 (Nov. 27) 1952.

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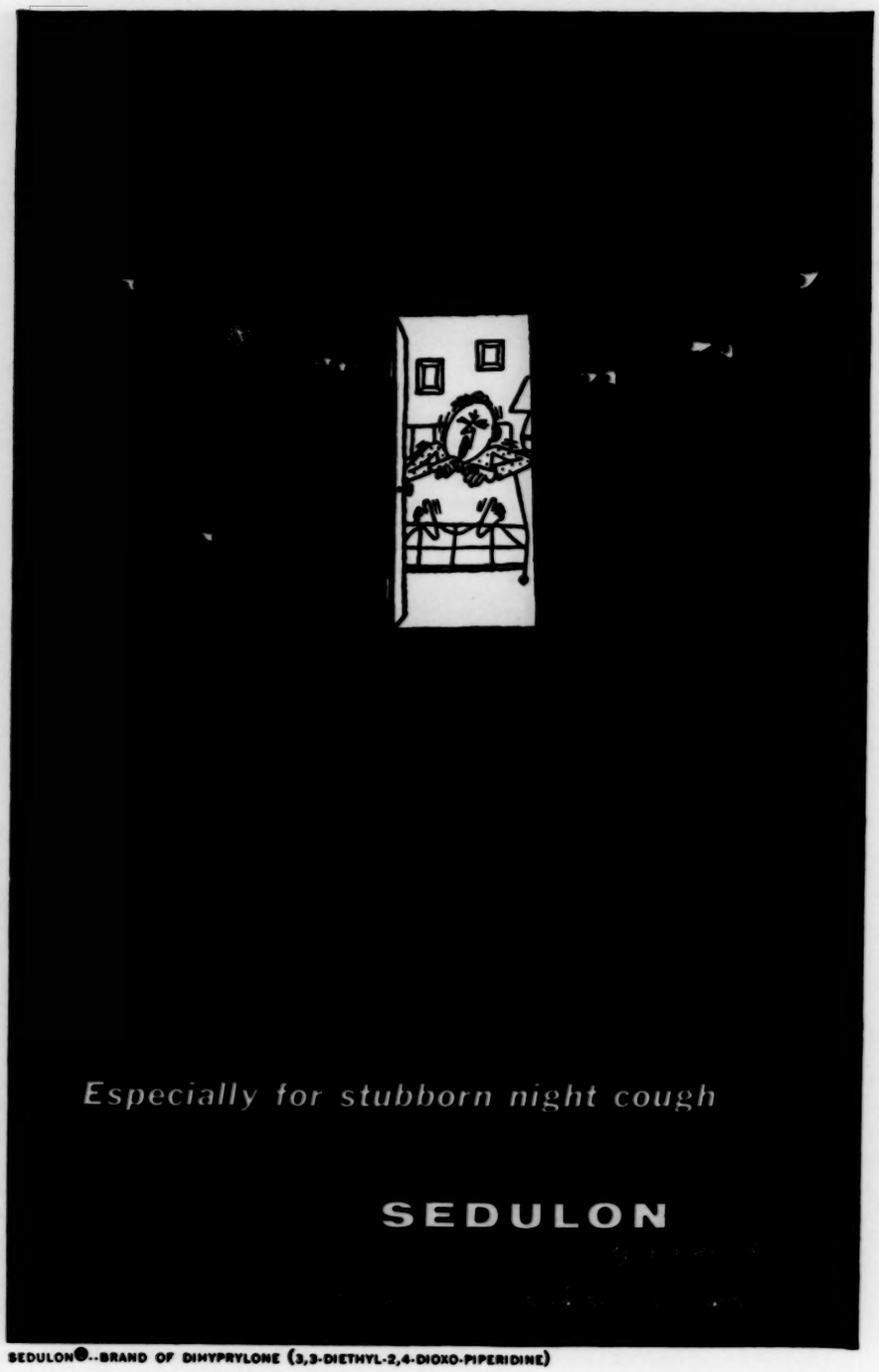

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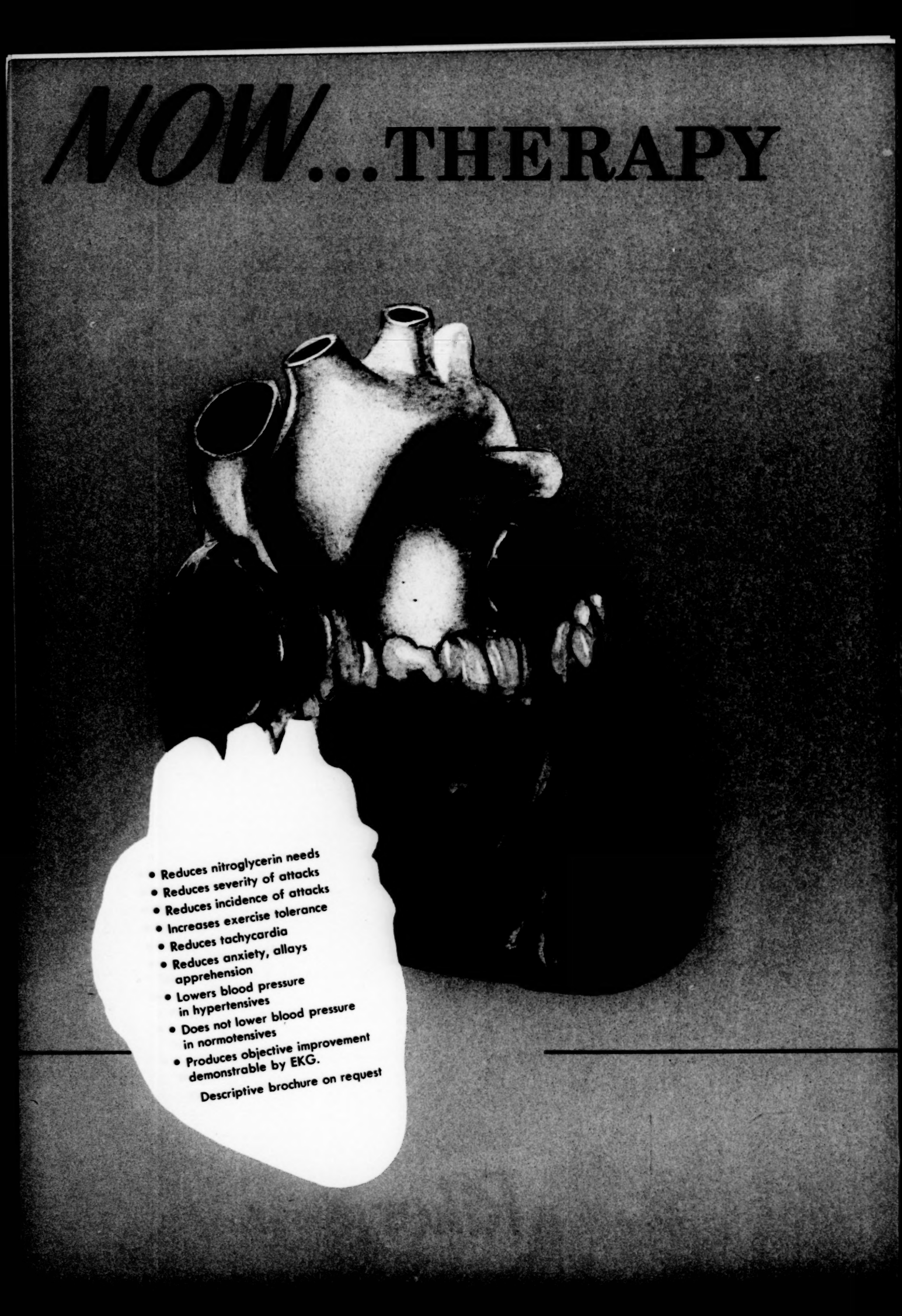

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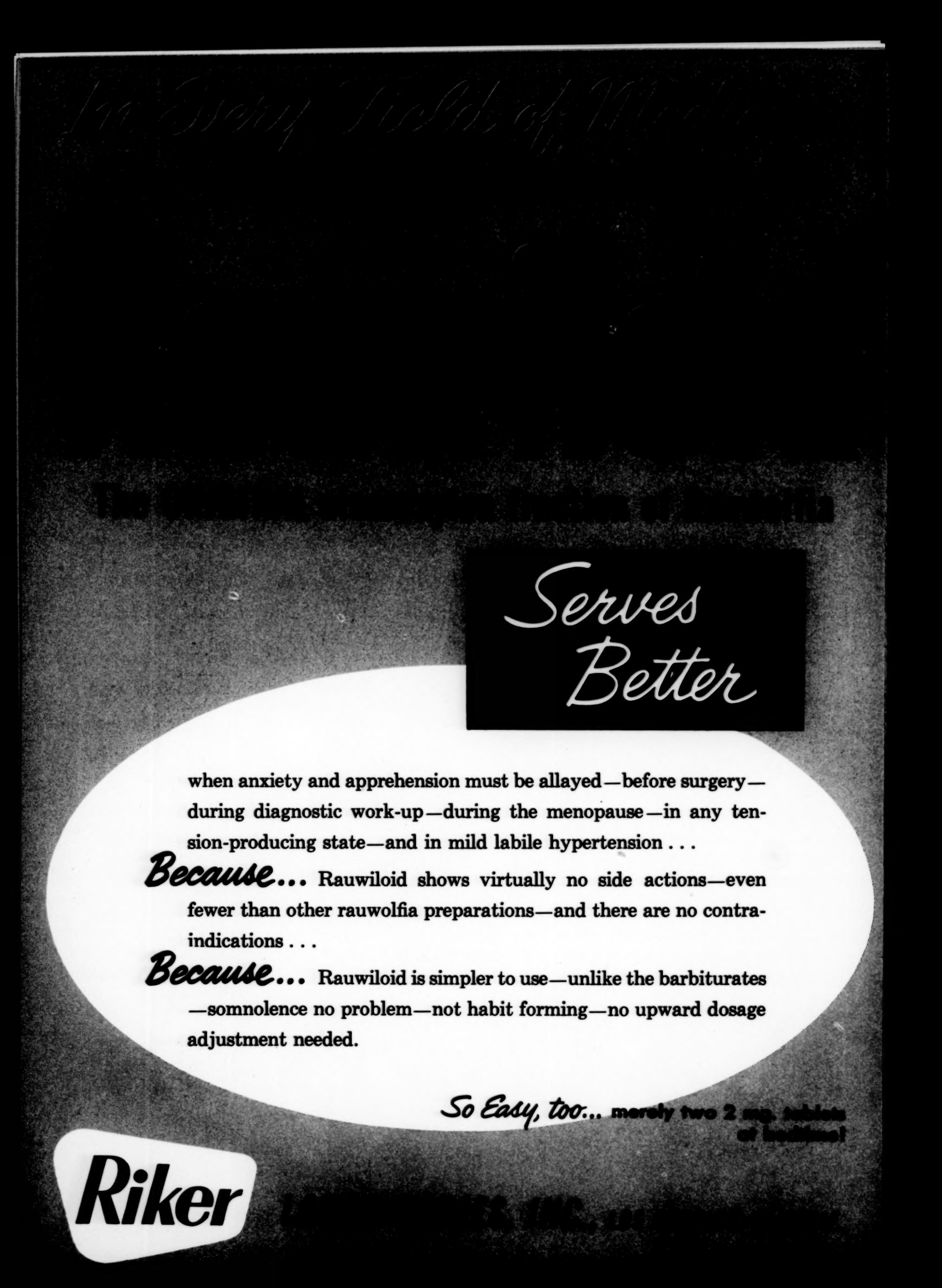
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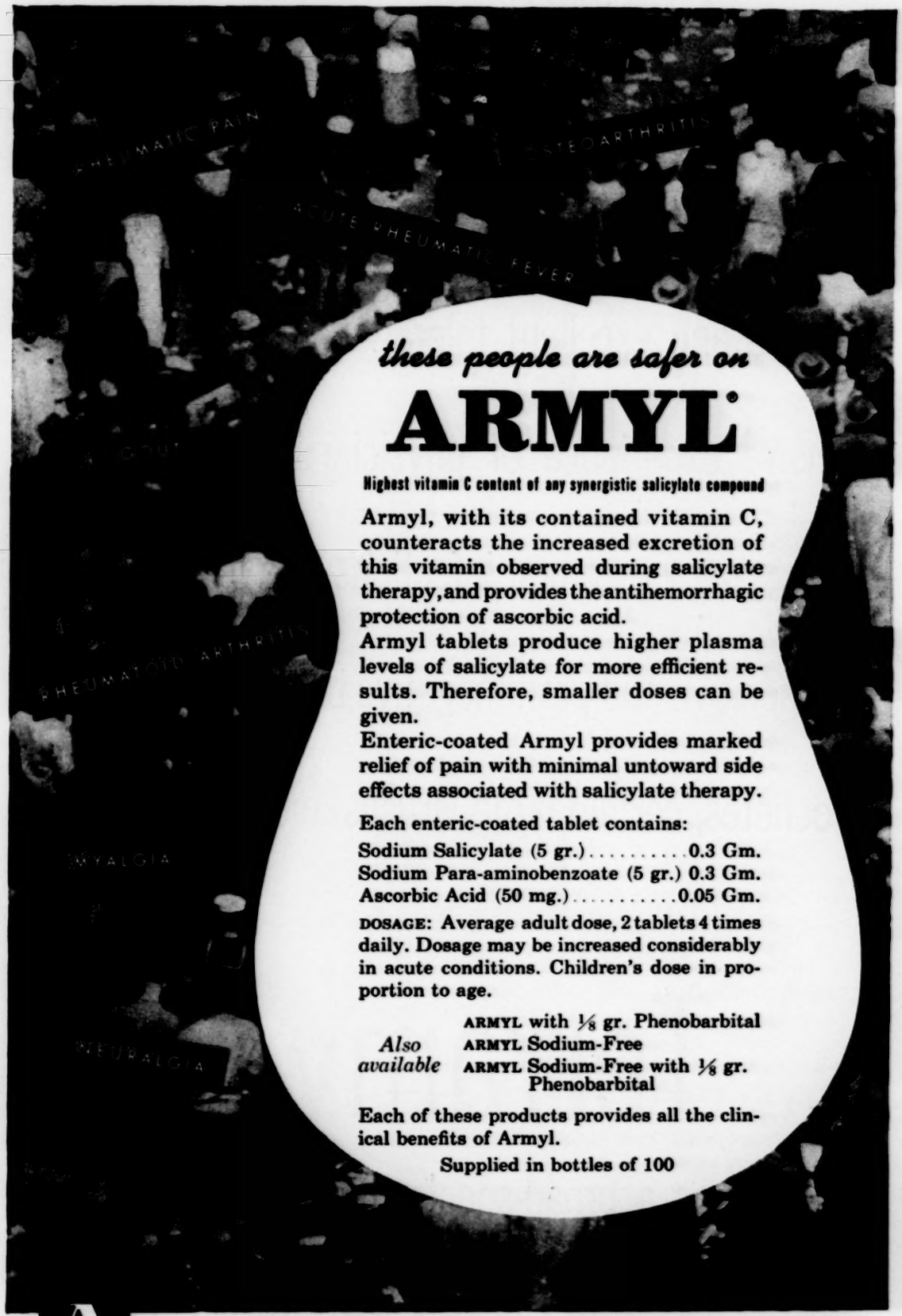

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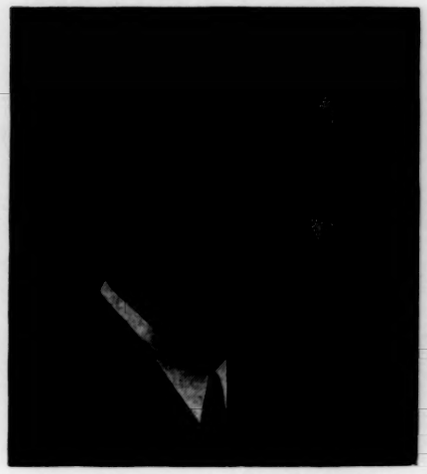
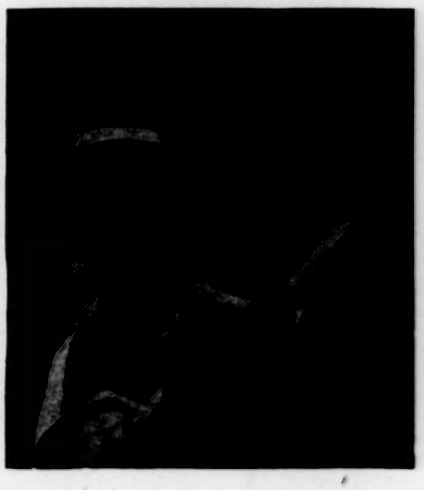


IN THE 40's AND 50's

"disease or body change is lurking in the background"† even though the individual may feel in good health. In this age group "Mediatric"* will help prevent premature atrophic changes due to waning sex hormone function and inadequate nutrition.



IN THE 60's AND 70's

involutional changes become increasingly apparent as the body loses its ability to resist environmental stress. "Mediatric"* will aid the aging economy cope more successfully with three important stressors: gonadal hormone imbalance, dietary insufficiency, and emotional instability.

IN THE 70's AND 80's

functional impairment is at its peak and, in most cases, is the end result of progressive disorders which had their onset in the forties. Patients treated with "Mediatric"* have responded with increased physical vigor, improved muscle tone, and better emotional balance.

†Kountz, W. B.: J.A.M.A. *153*:777 (Oct. 31) 1953.

* **"MEDIATRIC"®**

Steroid-nutritional compound

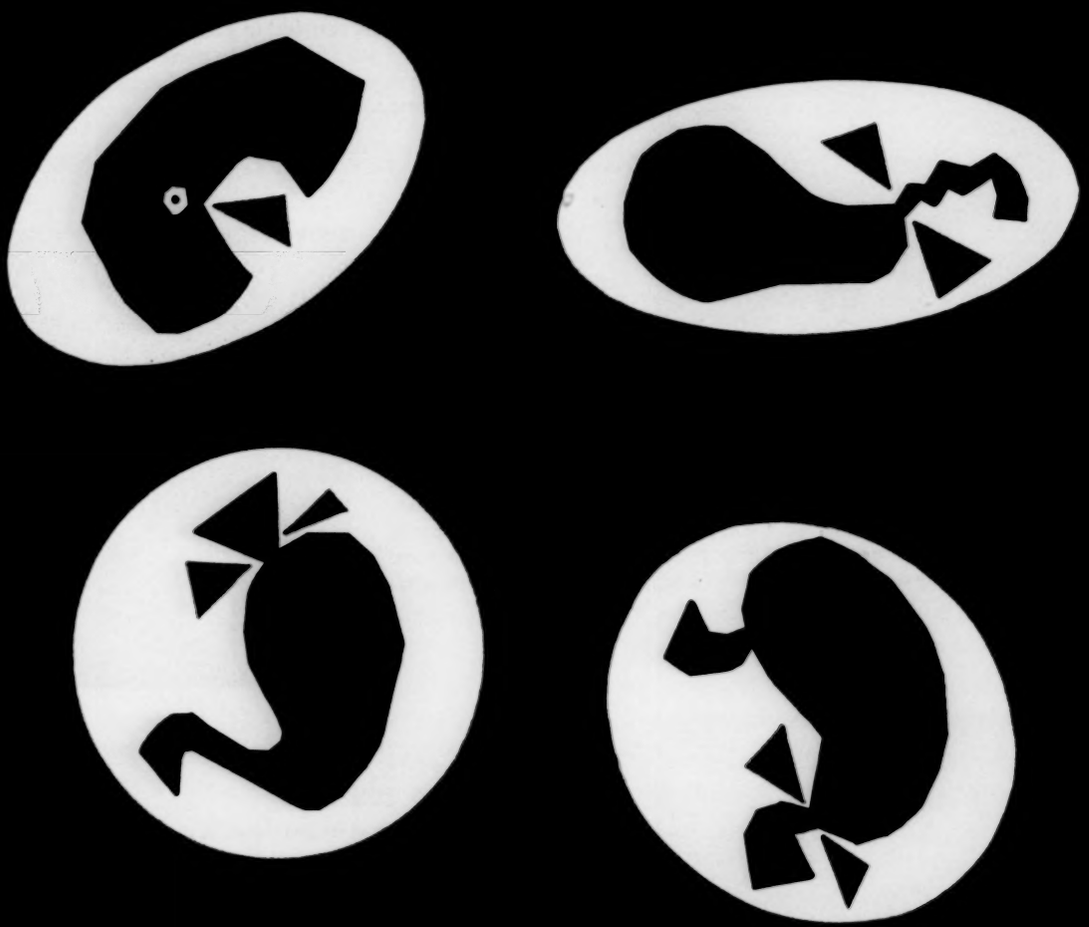
STEROIDS . . . to counteract declining sex hormone function
NUTRITIONAL SUPPLEMENTS . . . to meet the needs of the aging patient
A MILD ANTIDEPRESSANT . . . to promote a brighter mental outlook

Ayerst Laboratories
New York, N. Y., Montreal, Canada

Capsules, No. 252 — bottles of 30, 100, and 1,000.
Liquid, No. 910 — bottles of 16 fluidounces and 1 gallon.

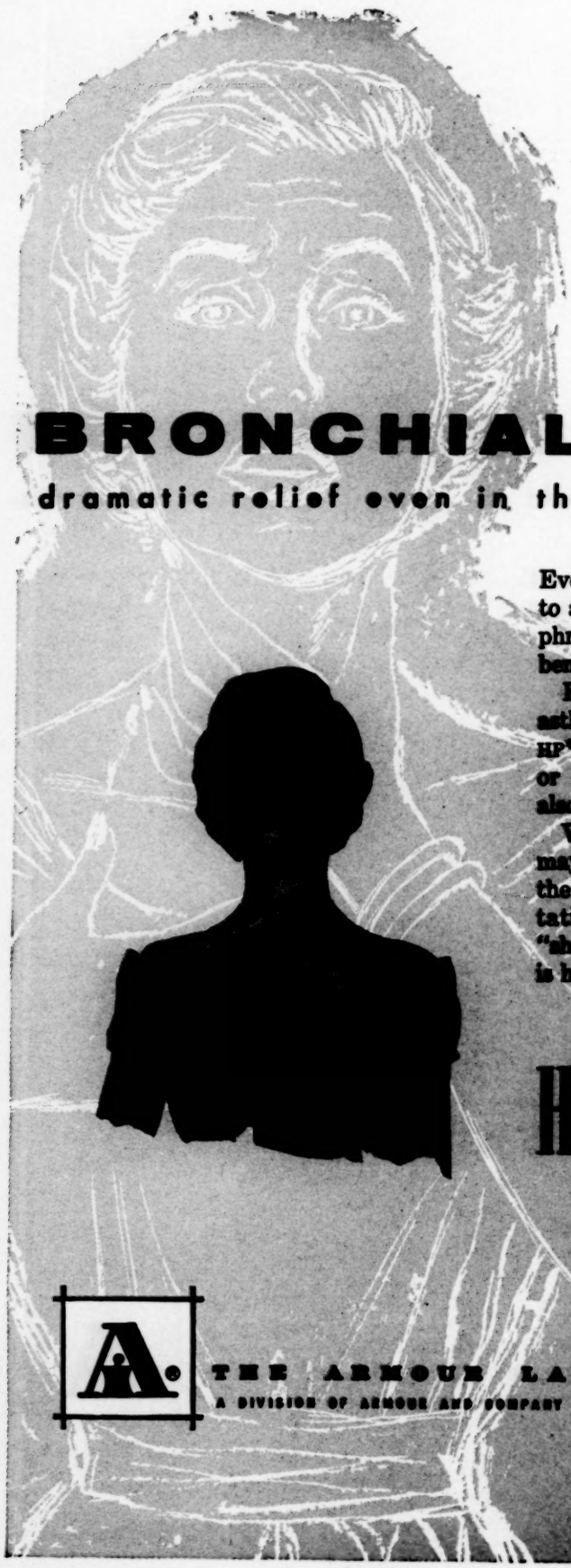
Average dosage, 1 capsule or 3 teaspoonfuls of liquid, daily.

rapid relief



DACTIL

new drug action



BRONCHIAL ASTHMA

dramatic relief even in the "refractory" patient

Even asthmatics who have proved refractory to all customary measures including epinephrine (and even to other forms of ACTH) may benefit dramatically from HP*ACTHAR *Gel*.

Fast relief in severe attacks of bronchial asthma can be confidently expected with HP*ACTHAR *Gel* given either subcutaneously or intramuscularly. HP*ACTHAR *Gel* may also provide long-lasting remissions.

When used early enough, HP*ACTHAR *Gel* may become a valuable agent in prolonging the life span of the asthmatic. The authoritative Journal of Allergy stresses: ACTH "should not be withheld until the situation is hopeless." [1]

1. Editorial, J. Allergy 23: 279, 1952.

HP* ACTHAR *Gel*

(IN GELATIN)

*Highly Purified. HP*ACTHAR*Gel is The Armour Laboratories Brand of Purified Adrenocorticotropic Hormone—Corticotropin (ACTH).

THE ARMOUR LABORATORIES

A DIVISION OF ARMOUR AND COMPANY • CHICAGO 11, ILLINOIS

an advance in therapy of adrenocortical insufficiency

Percorten® trimethylacetate

DESOXYCORTICOSTERONE TRIMETHYLACETATE CIBA

Intramuscular repository

"A month's therapy with a single injection." Therapy of chronic adrenocortical insufficiency has been improved and made more convenient to both patient and physician by Ciba's introduction of Percorten trimethylacetate in the form of a long-acting microcrystalline suspension.[1-5] • A single injection of this new long-acting steroid hormone derivative provides maintenance therapy for about a month. • This protracted and constant therapeutic effect is achieved because the suspension, when administered by deep intramuscular injection, simulates a miniature pellet in that a small fraction of the total dose is absorbed daily. • Patients who have Addison's disease and who are not in crisis can now be treated on a highly satisfactory ambulatory basis.

Indications: Chronic primary and secondary adrenocortical insufficiency, and hypotension associated with adrenal insufficiency. **Supplied:** Multiple-dose vials—4 ml. containing 25 mg./ml. as an aqueous suspension for intramuscular use only. **Note:** Percorten (desoxycorticosterone Ciba) is available in 4 administration forms: (1) Percorten trimethylacetate, long-acting intramuscular repository, aqueous suspension; (2) Percorten acetate in oil solution, for intramuscular injection; (3) Percorten acetate Linguets,® for sublingual or parabuccal absorption; (4) Percorten acetate pellets, for subcutaneous implantation.

Ask your Ciba professional service representative or write the Medical Service Division for complete information on the use of Percorten trimethylacetate.

1. Gross, F., and Tschopp, E.: Experientia *8*:75, 1952. 2. Thorn, G. W., and Jenkins, D.: In press. 3. Thorn, G. W.; Jenkins, D.; Arons, W. L., and Frawley, T. F.: Schweiz. med. Wchnschr. *82*:697, 1952. 4. Gaunt, R.; Leathem, J.; Howell, C., and Antonchak, N.: Endocrinology *50*:521, 1952. 5. Sorkin, S. Z., and Soffer, L. J.: Am. Fed. Clin. Research, May 4, 1952.

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BASIC IN ALL GRADES OF ESSENTIAL HYPERTENSION

Crystoserpine

CRYSTALLINE RESERPINE, DORSEY

now regarded as the chief active principle of Rauwolfia Serpentina*

Increasing experience continues to show that Rauwolfia serpentina is as basic in essential hypertension as digitalis is in congestive heart failure. Furthermore, recent evidence* demonstrates that reserpine possesses the unique antihypertensive, sedative, and bradycrotic properties characteristic of this unusual drug. On the basis of this study, reserpine is regarded by these investigators as the chief active principle of Rauwolfia serpentina.

Crystoserpine—reserpine, Dorsey—is valuable in all grades of essential hypertension. In the milder forms and in labile hypertension, it usually suffices alone. In the more severe forms, it reduces the amounts required of more potent antihypertensive agents.

In addition to lowering the blood pressure through central action, Crystoserpine induces a state of calm tranquility. Emotional tension is eased, the outlook improved.

There are no known contraindications to Crystoserpine. Average dose, 0.25 mg. to 1.0 mg. daily. Supplied in 0.25 mg. scored tablets.

* Wilkins, R. W.; Judson, W. E.; Stone, R. W.; Hollander, William; Huckabee, W. E., and Friedman, I. H.: Reserpine in the Treatment of Hypertension: A Note on the Relative Dosage and Effects, New England J. Med. 250:477 (March 18) 1954.

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Thoroughbreds are born, not made—

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POLYCYCLINE SUSPENSION '250'

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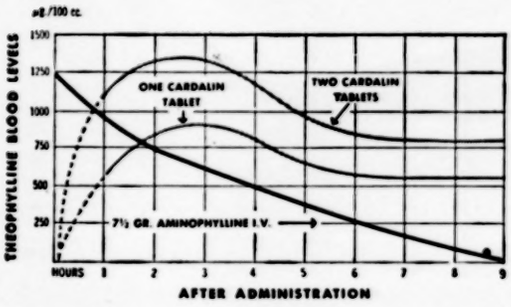
EVEN MORE EFFECTIVE ORALLY

Than Aminophylline Intravenously

Now you can give 5 grains of aminophylline orally with better results and complete safety. Of the oral aminophyllines, only Cardalin produces higher and better sustained blood levels than those attained with the customary intravenous dose of 7½ grains.



(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11: 301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100: 309, 1950.)

Bickerman, et al.[1] found that "the plasma theophylline levels on 300 and 600 mg. of Cardalin (1 and 2 tablets) revealed appreciable concentrations of theophylline in the circulating blood as long as seven hours after administration."

Aminophylline, an excellent drug, had to be made effective and practical orally. One of the principal problems of aminophylline has been that of administration. A small oral dosage of 1½ gr. or even 3 gr. does not produce theophylline blood levels high enough to accomplish the therapeutic objective. Attempts to achieve significant plasma theophylline levels with higher oral dosage failed because of the high incidence of nausea and vomiting.

Cardalin

tablets

Irwin-Neisler research teams worked on the formulation of an oral dosage of aminophylline which would be therapeutically effective and well tolerated by the majority of cases under intensive treatment. For the first time, the highest concentration of aminophylline for oral administration is supplied in Cardalin tablets. By the use of *two* protective factors, Cardalin enables the physician to administer high doses of aminophylline with a comparatively low incidence of gastrointestinal disturbance.

Each Cardalin Tablet contains:

Aminophylline.....5.0 gr.
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Ethyl Aminobenzoate.....0.5 gr.

Supplied: Bottles of 50, 100, 500 and 1000.

Also available **Cardalin-Phen** containing ¼ gr. phenobarbital per tablet.

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1. Bickerman, H. A., et al.: Ann. Allergy 11: 301, 1953.

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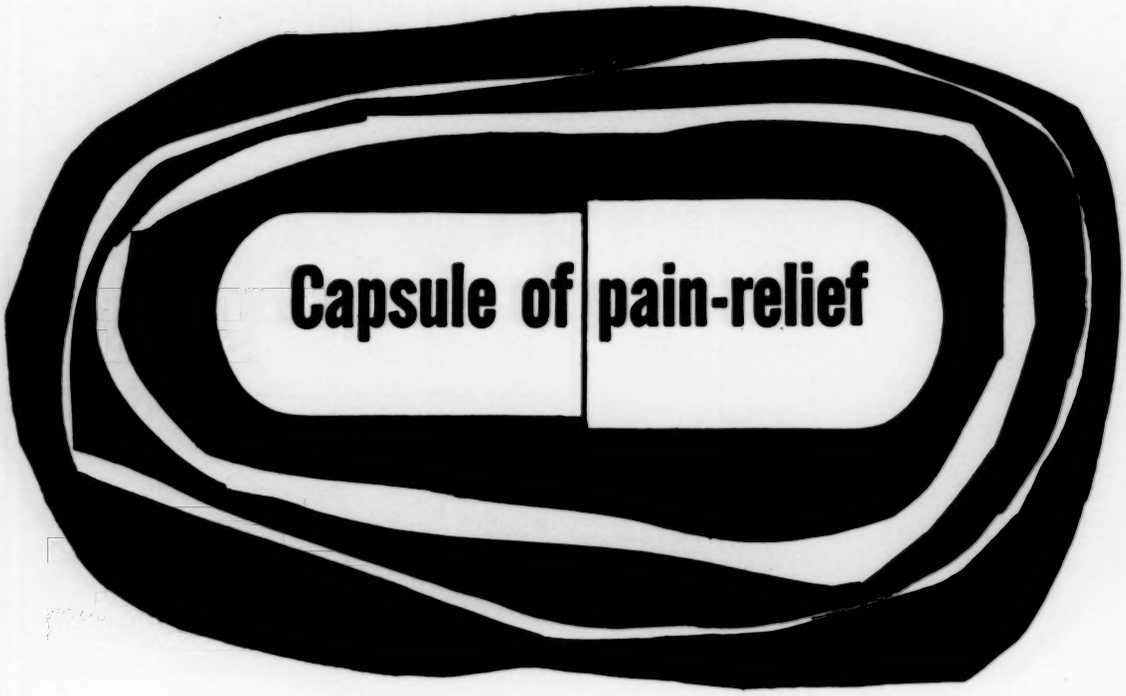

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Convenient dosage—two strengths

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Codeine Phosphate	gr. ¼
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Acetophenetidin	gr. 2½
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Current reports[1,2] describe the increasing incidence of resistance among many pathogenic strains of microorganisms to some of the antibiotics commonly in use. Because this phenomenon is often less marked following administration of CHLOROMYCETIN (chloramphenicol, Parke-Davis), this notably effective, broad spectrum antibiotic is frequently effective where other antibiotics fail.

Coliform bacilli—100 strains

up to 43% resistant to other antibiotics;
2% resistant to CHLOROMYCETIN.[1]

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2.4% resistant to CHLOROMYCETIN.[2]

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

References
(1) Kirby, W. M. M.; Waddington, W. S., & Doornink, G. M.: Antibiotics Annual, 1953-1954, New York, Medical Encyclopedia, Inc., 1953, p. 285. (2) Finland, M., & Haight, T. H.: *Arch. Int. Med.* 91: 143, 1953.

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Significant notes on another value found in the meaty parts of fresh oranges...

The Citrus Bioflavonoids

Continuing studies on the citrus bioflavonoids, extensively supported by Sunkist Growers over the past 18 years,* are building conclusive evidence of the values of these materials, especially to the capillary system. It is becoming increasingly apparent that the citrus bioflavonoids, particularly hesperidin, play an essential role in nutrition both in health and disease.

Research indicates the bioflavonoids strengthen the capillary walls and thus aid in the maintenance of normal capillary permeability and integrity. And they are now indicated in many disease states having, in common, impaired capillary function. These include habitual abortion[1], rheumatic fever[2], rheumatoid arthritis[3], psoriasis[4], hypertension[5], respiratory disease[6], and possibly radiation injury.

The citrus bioflavonoids, like pro-vitamin A and the newly-recognized protopectins, are found mainly in the meaty parts of oranges (the cell walls and fibrous tissues) rather than the juice. In fact, the whole peeled orange contains 10 times as much bioflavonoid (hesperidin) as the finely-strained juice alone.

The bioflavonoids are another important reason for the trend to the *fresh orange* ... fresh oranges for eating and whole fresh orange juice with a good portion of the healthful solids left in it. (For therapeutic use, the daily dietary intake of fresh oranges can be supplemented with medicinal products derived from citrus.)

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Sunkist Oranges are recognized as the finest oranges obtainable in any market... anywhere.

* Some of the earliest scientific papers on the structure, chemical and physical properties, physiological and pharmacological studies on purified bioflavonoid materials were conducted in the research laboratories of Sunkist Growers and under clinical fellowships supported in whole or in part by Sunkist.

Since the clinical importance of citrus bioflavonoids was highlighted by Nobel Laureate Szent-Györgyi in 1936, more than 600 scientific papers have been published in this field. A complete bibliography will be mailed on request.

1 *Greenblatt, Robert B.*, Obstetrics and Gynecology, 2:530, November 1953.
Javert, Carl T., Obstetrics and Gynecology, 3:420, April 1954.

2 *Rinehart, J. F.*, J. Clin. Invest., 23:941, 1944, Calif. Health, 1:163-6, 1944.

3 *Selsman, C. J. V.*, and S. Horoschak, Am. J. Dig. Dis., 17, 92, 1950.
Warter, P. J. et al, Delaware St. Med. J., 20:41, 1948.

4 *Goldfarb, A. E.*, Arch. Dermat. and Syphil., 43:536-8, 1941. Med. World (London) 63:29, 1945.

5 *Barlshaw, S. B.*, Exptl. Med. Surg., 7, 35, 1949.
Selsman, C. J. V., and S. Horoschak, Am. J. Dig. Dis., 17, 92, 1950.

6 *Getz, H. R.*, Milbank Foundation, 1950.
Biskind, M. S., and Martin, Wm. C., Am. J. Dig. Dis., 21:177, July 1954,

In Myocardial Infarction

C·R·P·A*

C-Reactive-Protein Antiserum — Schieffelin

A highly sensitive test for presence of inflammation

- Investigators have found this test to be consistently negative in cases of cardiac insufficiency uncomplicated by myocardial infarction and inflammation.[1,4]
- based upon presence of specific C-reactive protein in serum of patients with certain inflammatory diseases — characteristic precipitin reaction develops upon addition of C·R·P·A to serum of such patients . . . C-reactive protein is never found in normal serum.[2]
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For detailed instructions on the materials and techniques required for the use of C·R·P·A — Schieffelin, just send us a request and we will mail you a descriptive brochure.

1. Kroop, I. G. and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:93 (May) 1954.
2. Wood, H. F., and McCarty, M.: J. Clin. Investigation 30:616 (June) 1951.
3. Stollerman, G. H., et al.: Am. J. Med. 15:645 (Nov.) 1953.
4. Hedlund, P.: Acta med. Scandinav., Supplement 196:579, 1947.

Supplied: 1 cc. vials (30-40 determinations)

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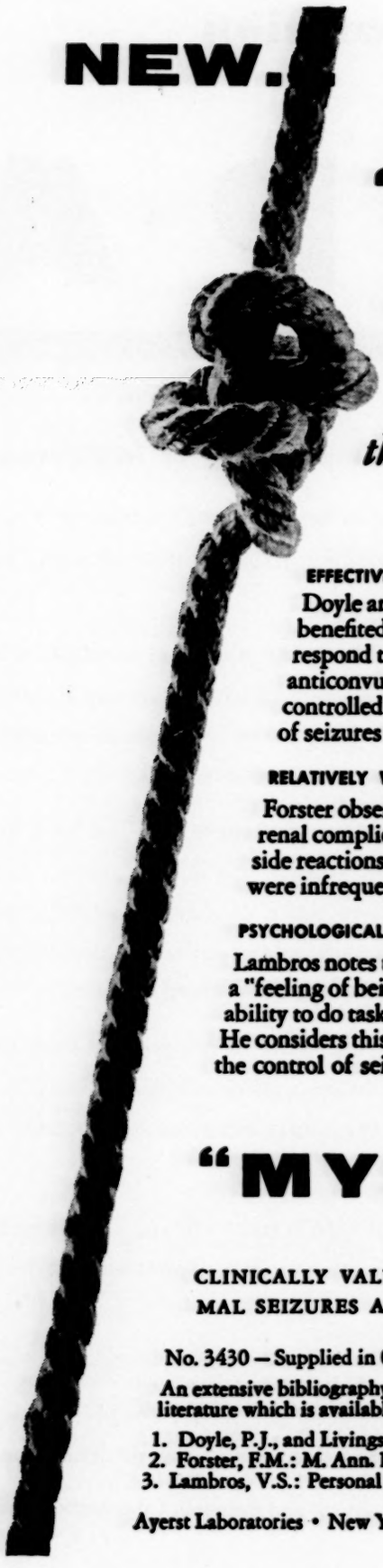

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Doyle and Livingston report that 63 of 100 patients benefited from "Mysoline" therapy after they had failed to respond to maximum dosages of other anticonvulsants for at least one year. Seizures were completely controlled in 30 and the number of seizures was markedly reduced in 20.[1]

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No. 3430 — Supplied in 0.25 Gm. tablets (scored), bottles of 100 and 1,000.

An extensive bibliography supporting the value of "Mysoline" is included in the literature which is available to physicians upon request.

1. Doyle, P.J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Forster, F.M.: M. Ann. District of Columbia *23*:137 (Mar.) 1954.
3. Lambros, V.S.: Personal Communication.

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Is there an engineer in the waiting room?

You, as a physician, are thoroughly trained and experienced in detecting the clinical conditions that affect your patients' physical being. They depend on you completely for a knowledge and guidance not possessed by themselves. Conversely, do you not similarly look to professional men in other fields for aid when the need arises?

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SUPPLIED: Vials of 12 and bottles of 100.

REFERENCE: 1. J. Pediat. 42:292 (March) 1953.

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Patients can lose weight and maintain a restricted diet, in comfort, without undesirable side effects . . .

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Obedrin offers the full anorexigenic value of Methamphetamine to curb the desire for food, while counteracting mood depression. Patient co-operation is made easier.

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Large doses of Ascorbic Acid aid in the mobilization of fluids, so often an obstacle in obesity.

BULK NOT NECESSARY

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Niacin	5 mg.

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NEW DOSAGE FORM

- affords prompt control in a wide range of infections
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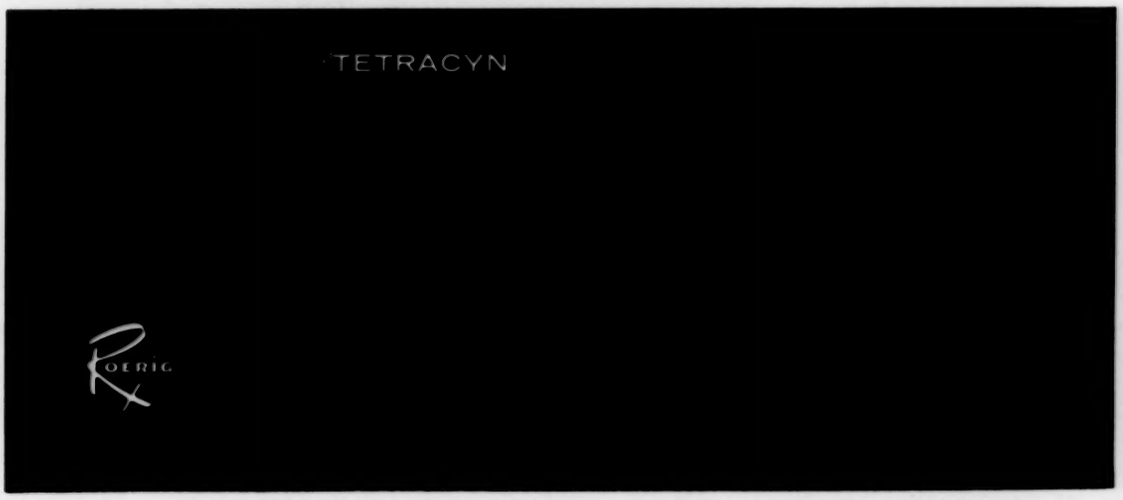
- keeps control of therapy in the hands of the physician

SUPPLIED: Vials of 100 mg.



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Three antibiotics in potentiating action . . . WYBIOTIC Troches are formulated for wide-range bactericidal action with extraordinary freedom from sensitization and bacterial resistance. For non-febrile mouth and throat infections, both gram-negative and gram-positive. No danger of sensitizing the patient to antibiotics that may be needed systemically in later serious illness, nor of developing in him resistance to these antibiotics.

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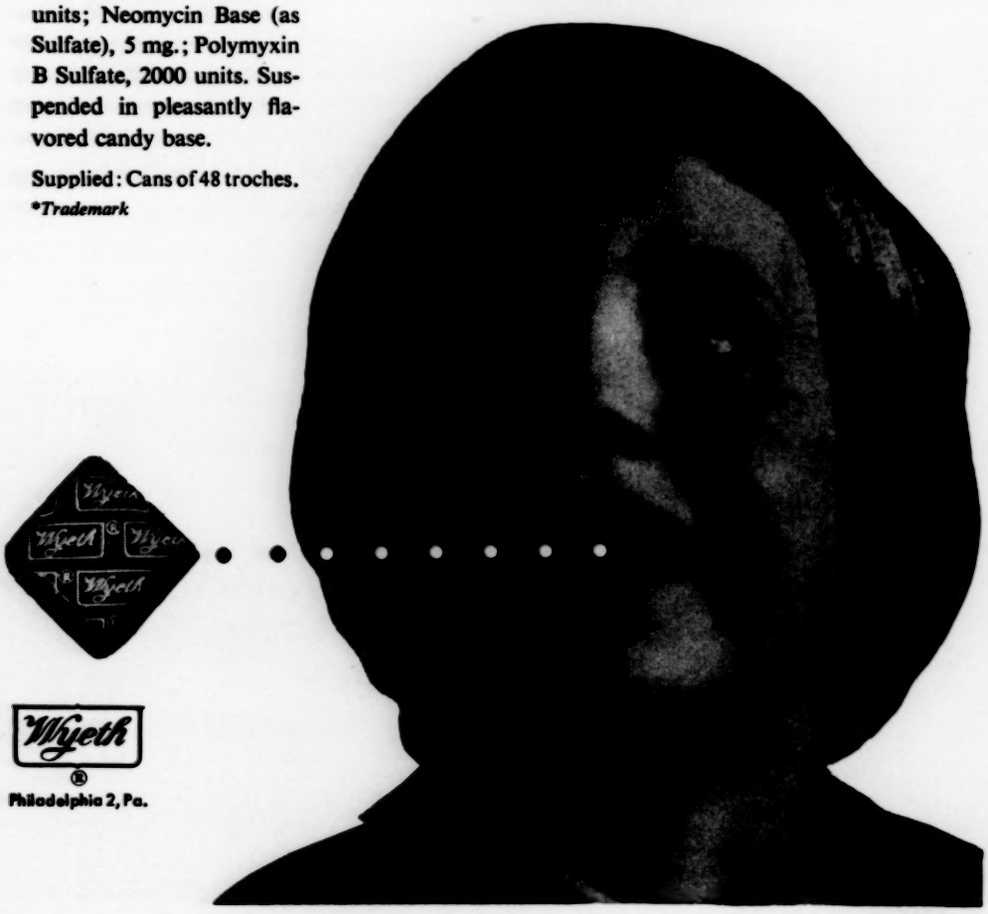

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Estrogenic Substances* .. 1 mg.
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**Naturally-occurring equine estrogens (consisting primarily of estrone, with small amounts of equilin and equilenin, and possible traces of estradiol) physiologically equivalent to 1 mg. of estrone.*

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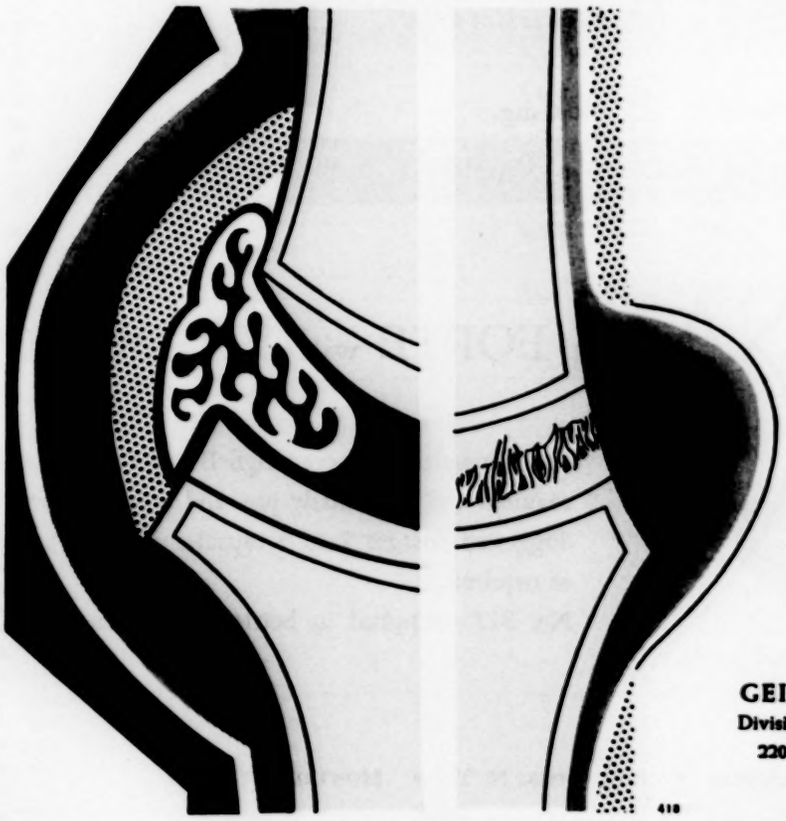

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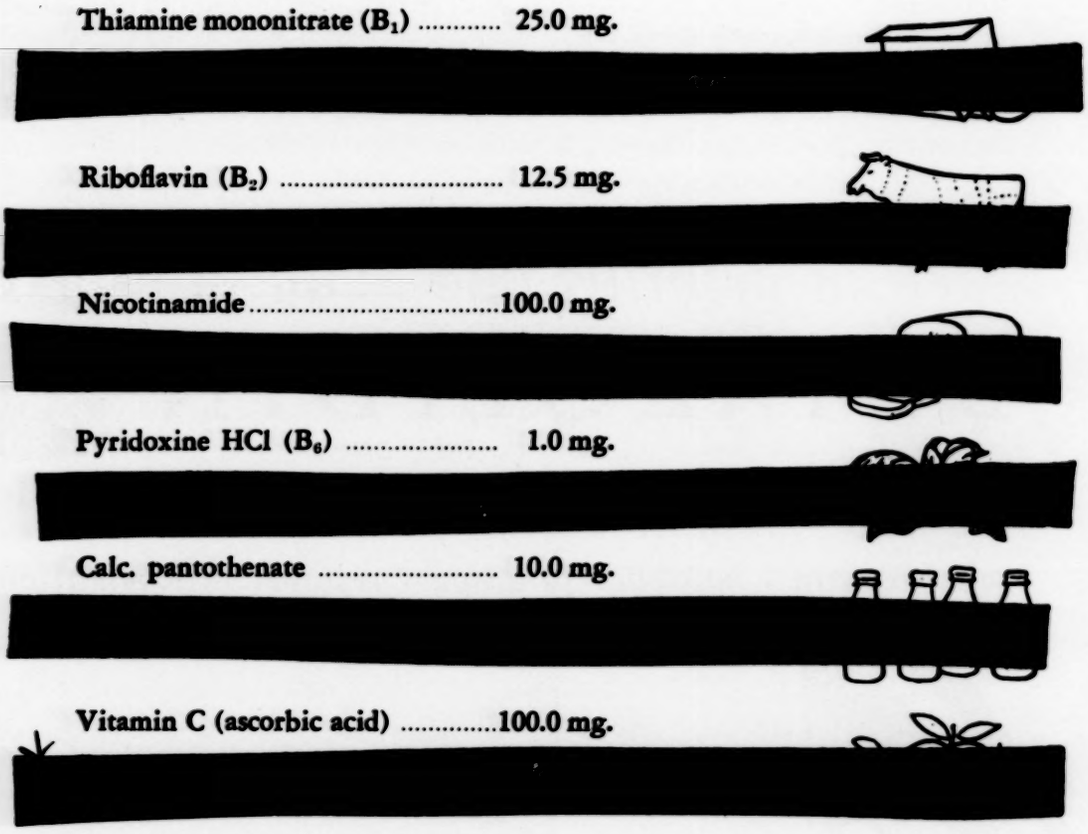

Thiamine mononitrate (B_1) ..... 25.0 mg.

Riboflavin (B_2) ..... 12.5 mg.

Nicotinamide ..... 100.0 mg.

Pyridoxine HCl (B_6) ..... 1.0 mg.

Calc. pantothenate ..... 10.0 mg.

Vitamin C (ascorbic acid) ..... 100.0 mg.

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Recommended whenever high B and C levels are required and particularly pre- and postoperatively. Suggested dosage: 1 to 3 capsules daily, or more as required.

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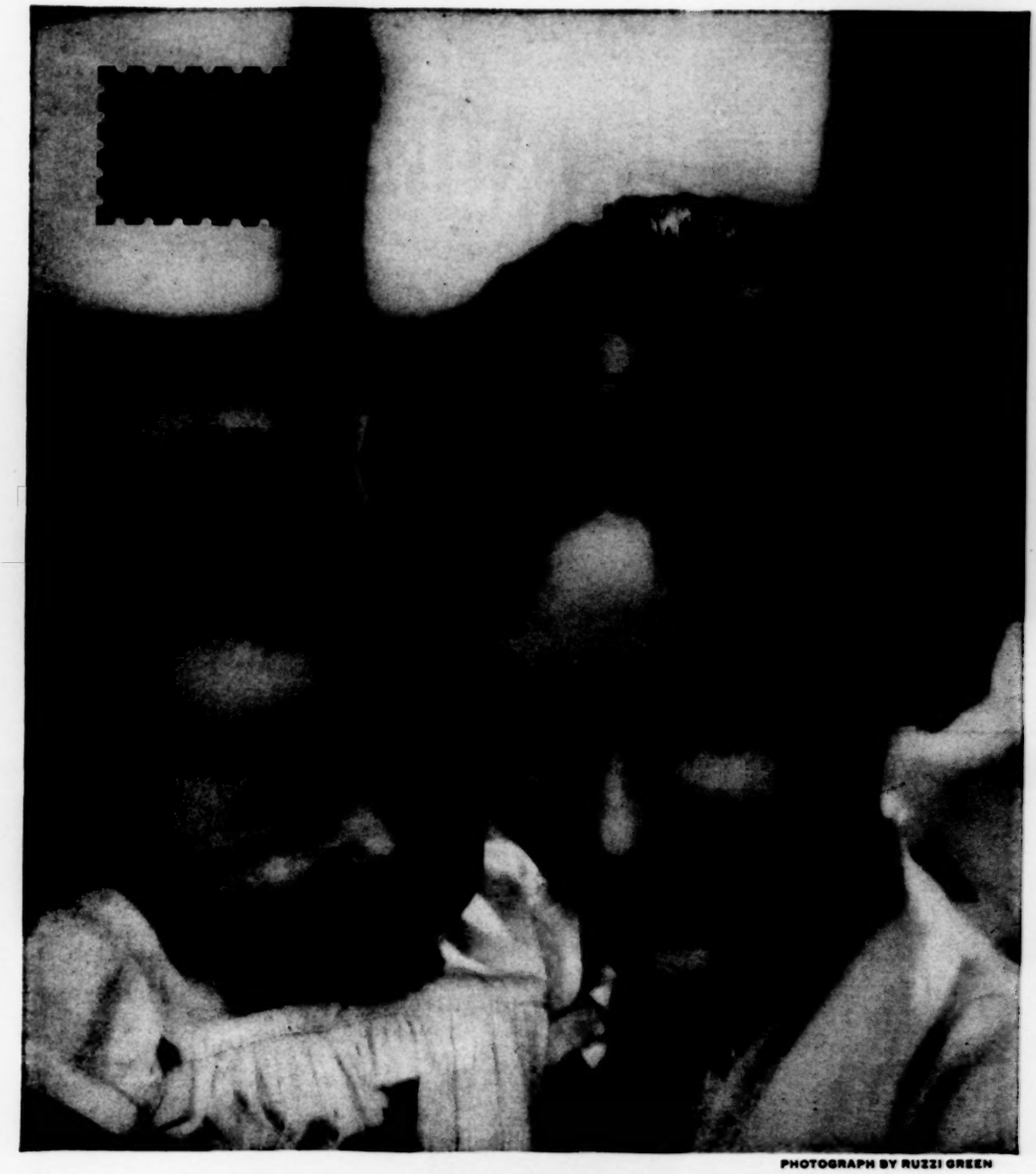

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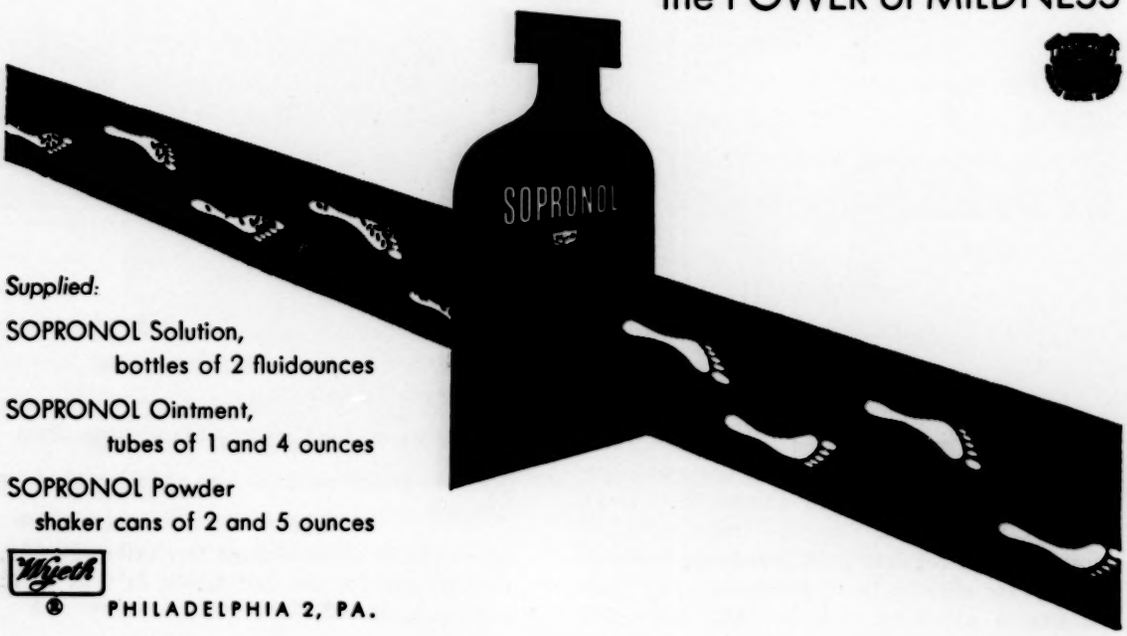

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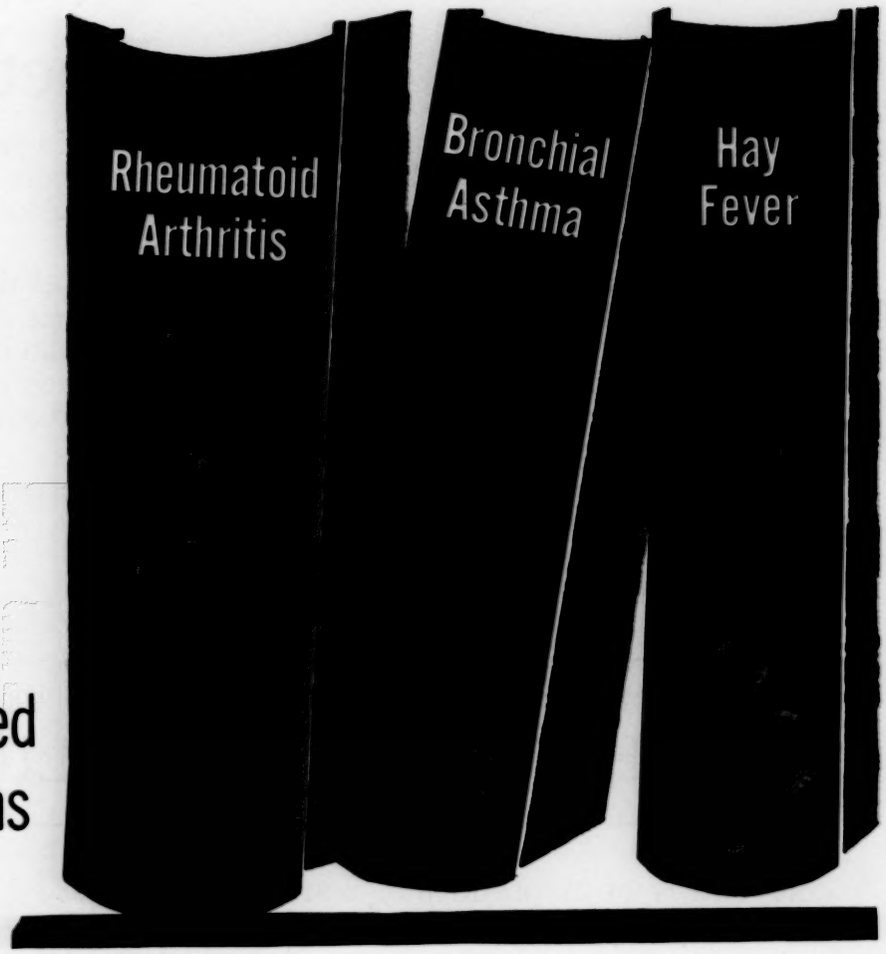

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references: 1. Boland, E. W., and Headley, N. E.: J.A.M.A. 148:981, March 22, 1952. 2. Schwartz, E.: J. Allergy 25:112-119, March, 1954.

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References:

1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: N. Y. State J. Med. *52*:2012 (Aug. 15) 1952.

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